In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. [redacted]V
January 16, 2009
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To be Published

JANE DOE/28,	*	
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Petitioner,	*	
	*	Entitlement; causation of
v.	*	nonspecific arthritis one month
	*	after third hepatitis B vaccination
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Clifford J. Shoemaker, Vienna, VA, for petitioner.
Glenn A. MacLeod, Michael J. Milmoe, Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioner filed a petition dated May 30, 2000, under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that hepatitis B vaccinations in April and May

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision is filed, petitioner has 14 days to identify and move to 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. Petitioner moved to redact her name from this decision. The undersigned grants this motion.

1998 caused an unspecified adverse reaction. On that date, chief special master Gary Golkiewicz assigned the case to former special master John Edwards. On June 6, 2000, the chief special master assigned the case to himself. On April 5, 2001, the chief special master assigned the case to special master Richard Abell. On August 14, 2001, special master Abell granted petitioner's motion for authority to issue subpoenas to obtain medical records.

On July 19, 2002, petitioner moved for a stay of proceedings in the case in order to participate in a hepatitis B steering committee intended to develop expert testimony. On December 5, 2002, the chief special master reassigned the case back to himself. On March 17, 2005, petitioner filed a status report stating there were still medical records outstanding and counsel was still looking for an expert.

On July 17, 2006, the chief special master reassigned the case to special master Denise Vowell.

On October 18, 2006, petitioner filed an expert report from Dr. Yehuda Shoenfeld. P. Ex. 24.

On May 7, 2007, respondent filed an expert report from Dr. Alan Brenner. R. Ex. A.

On July 30, 2007, the chief special master reassigned the case to the undersigned.

On June 24, 2008, the undersigned held a hearing. Testifying for petitioner was Dr. Yehuda Shoenfeld, an immunologist. Testifying for respondent was Dr. Alan I. Brenner, a rheumatologist.

FACTS

Petitioner was born on March 16, 1965.

In May or June 1993, when petitioner was two weeks pregnant, she received her first hepatitis B vaccination, according to the records of Dr. Donald Gilver. Med. recs. at Ex. 2, p. 83.

There is no documentation of petitioner's second and third hepatitis B vaccinations except for a communication dated May 15, 2006 from her father, a dentist, who employed petitioner, that he saw her receive hepatitis B vaccine in his office on April 3, 1998 and May 8, 1998. Med. recs. at Ex. 22. Her father states the vaccine was purchased (he does not state by whom) at St. Francis Hospital in Monroe, Louisiana, where his dental office is located, and that registered nurse Anita Holdiness administered the vaccinations. *Id.*

On June 9, 1998, one months after petitioner's third hepatitis B vaccination, petitioner saw Dr. Kerry L. Anders, complaining of pain in the right knee for two days and pain in her neck. She had had a rash for two days. She had a low grade temperature the prior night of 100.2º and, that morning, 100.3º. Med. recs. at Ex. 6, p. 32. X-rays showed osteoarthritis of the cervical spine and right knee. Dr. Anders prescribed Ampicillin, Celestone, and Rocephin. *Id.*

On June 10, 1998, petitioner returned to Dr. Anders and said she was better. Her temperature was down to 100º. Her hips and legs were sore. She had more range of motion of her neck and her sore throat was better. Med. recs. at Ex. 6, p. 31. Dr. Anders' impression was improved pharyngitis. *Id.*

On June 11, 1998, petitioner was admitted to Columbia North Monroe Hospital. Med. recs. at Ex. 14, p. 11. Dr. Anders noted that petitioner's hips were extremely sore and her arms were sore. Her white count in his office was 30,000. She had a temperature of 100.5º. Dr. Anders' assessment was febrile illness with new onset multiple pain. Med. recs. at Ex. 6, p. 128.

On June 12, 1998, Dr. Madura Rangaraj wrote a consultation that petitioner had fever and polyarthritis, markedly elevated sedimentation rate, and leukocytosis with a white count of 21,000. On Monday, June 8, 1998, petitioner noticed fairly significant pain in her right knee, went to Dr. Anders, and received a cortisone shot. She subsequently noticed a rash on the leg and then the armpits, and different joints had been bothering her including the right shoulder, the left wrist, the right hand, both knees, and occasionally the ankle and foot. In the hospital, she ran temperatures up to 102º. Her sedimentation rate was 73. Her white count was elevated to 21.5. At Dr. Anders' office on June 8, 1998, her white count was 18,000. Her antinuclear antibody (ANA) and rheumatoid factor remained negative. Her blood cultures were negative. *Id.* Dr. Rangaraj's impression was febrile polyarthritis, most likely viral. Med. recs. at Ex. 14, p. 11.

On June 20, 1998, Dr. Anthony LaRocco, Jr. wrote a consult. Med. recs. at Ex. 14, p. 9. Petitioner was in her usual state of good health until 12 to 14 days earlier (putting onset of symptoms at June 6 or 8, 1998), when she awoke with pain in her right knee which progressed. She also noted a rash on her arms and legs. She started having some fever with muscle aches. She saw Dr. Anders the next day, June 11, 1998. Her white blood count was elevated at 18,000. She received Celestone, Rocephin, and a prescription for oral Ampicillin. She came back the following day and was given another shot of Rocephin. By June 11, 1998, she continued to have muscle aches and her white count was up to 30,000. She was admitted for further evaluation and therapy. She had intermittent moderate grade fevers and multiple joint pains. *Id.* Petitioner had had some pharyngitis. Med. recs. at Ex. 14, p. 8. She had a vaginal yeast infection. She weighed 204 pounds. Her temperature was 101.5 º. She had a macular and vaguely papular erythematous rash mostly on the proximal medial aspects of her extremities. *Id.* Hepatitis B

core IgM and hepatitis B surface antigen were negative. Throat culture was remarkable for some beta strep. Vaginal smear grew candida. Chest x-ray on June 15, 1998 showed left posterior basilar infiltrate consistent with pneumonia and improved slightly since June 13, 1998. *Id.*

On June 22, 1998, petitioner was discharged from Columbia North Monroe Hospital. Med. recs. at Ex. 6, p. 130. Dr. Anders wrote the discharge summary. Petitioner was hospitalized for fever, rash, joint pain, and pharyngitis. She had a two-week history of arthralgia, rash, fever, plus or minus pharyngitis, elevated white count, elevated sedimentation rate, positive throat culture per beta strep, and left lower lobe infection. *Id.* The differential diagnoses were acute parvovirus infection, mycoplasma pneumonii, other viral infections such as rickettsii and leptospirosis, rule out acute rheumatic fever, and rule out collagen vascular disease. *Id.*

On June 23, 1998, petitioner saw Dr. Anders. Med. recs. at Ex. 6, p. 30. Her rash had cleared. She still had some right wrist pain. She spiked a temperature that morning of 102º. Dr. Anders prescribed Prilosec for gastritis symptoms. *Id.*

On June 25, 1998, petitioner saw Dr. Anders for a febrile illness. Med. recs. at Ex. 6, p. 29. Her white count was still mid to high 30,000, but Dr. Anders thought that was from steroids. *Id.*

On June 26, 1998, petitioner saw Dr. Anders. She was better. Her ANA was negative and her white count was down from 38,000 the day before to 33,000. Dr. Anders continued petitioner on Medrol Dosepak and antibiotics. Med. recs. at Ex. 6, p. 28.

On June 29, 1998, petitioner saw Dr. Anders. Her white count was down to 31,000. Med. recs. at Ex. 6, p. 27.

On June 30, 1998, petitioner saw Dr. Anders. Her joint pain and rash were much better but she still had low grade fever. Med. recs. at Ex. 6, p. 26.

On July 3, 1998, petitioner saw Dr. Anders who diagnosed petitioner with resolving serum sickness.[2] Dr. Anders wrote: "Rule out hepatitis B related incident. She had the vaccine and then got ill after that. Her other workup has returned negative." Med. recs. at Ex. 6, p. 25. Petitioner's white count was down to 22,000. She still had fever at night, but not to the extent she had before hospitalization. The rash had resolved. Most of the joint pain had resolved. *Id.*

On July 10, 1998, petitioner saw Dr. Anders. She had right wrist pain and right upper quadrant abdominal discomfort. Her white count was down to 18,000. Med. recs. at Ex. 6, p. 24.

On July 13, 1998, petitioner saw Dr. Anders. She had a swollen right hand, left forefinger, and right foot. This was all consistent with possible rheumatoid arthritis (RA). Med. recs. at Ex. 6, p. 23.

On July 13, 1998, petitioner saw Dr. Rangaraj with significant difficulties. Med. recs. at Ex. 8, p. 35. Her hands and ankles had been bothering her. She had swelling in her hands and

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[2] Serum sickness is "a hypersensitivity reaction to the administration of foreign serum or serum proteins characterized by fever, urticaria, arthralgia, edema, and lymphadenopathy. It is caused by the formation of circulating antigen-antibody complexes that are deposited in tissues and trigger tissue injury mediated by complement and polymorphonuclear leukocytes. Serum sickness is classed with the Arthus reaction and other immune complex diseases as a type III hypersensitivity reaction (Gell and Coombs classification). Although serum sickness is now rare because of the replacement of most animal-derived antisera with human immune globulins, an identical illness (*serum sickness-like reaction* or *syndrome*) can be produced by hypersensitivity reactions to penicillin and other drugs." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1694.

ankles. Her knees started to bother her. She had been seronegative, but she looked more and more like a rheumatoid. *Id.*

On July 14, 1998, petitioner saw Dr. Anders for lab work. Med. recs. at Ex. 6, p. 22.

On July 23, 1998, petitioner saw Dr. Anders to follow up on lab results. Med. recs. at Ex. 6, p. 21.

On July 31, 1998, petitioner saw Dr Robert E. Goodman, a rheumatologist, for a second opinion. Med. recs. at Ex. 16, p. 8. She had her second hepatitis B vaccination in May 1998. In late May and early June, she developed a febrile illness with swollen joints, a faint skin rash, and elevated white count. She was 5'6" tall and weighed 199 pounds. *Id.* Dr. Goodman's assessment was inflammatory polyarthritis with negative rheumatoid factor and ANA. His differential diagnosis included serum sickness and seronegative RA. Med. recs. at Ex. 16, p. 9.

On August 10, 1998, petitioner saw Dr. Anders. Her white count was 13.6. Dr. Anders wrote: "Inflammatory polyarthritis inflammation of many joints. Possible cause, rheumatoid arthritis, allergic reaction to Hepatitis B vaccine with resultant serum sickness. Lupus unlikely, or scoriatic arthritis unlikely." Med. recs. at Ex. 6, p. 19.

On April 7, 1999, petitioner saw Dr. Ronald L. Ellis at the St. Francis Chronic Pain Management Center. Med. recs. at Ex. 17, p. 78. Petitioner had a history of multiple joint pain that began spontaneously in June 1998, originally in the right knee. Two days after onset, the pain spread to multiple joints. She had two hepatitis B vaccinations, one in April and the other in May, preceding the onset of her pain. *Id.* Dr. Ellis' assessment was: (1) history of serum

sickness after hepatitis B vaccination in 1998; (2) allergic arthropathy[3] with multiple joint pain secondary to #1. Med. recs. at Ex. 17, p. 80.

On July 27, 1999, petitioner had an electromyography (EMG) and nerve conduction velocity (NCV) study done. Med. recs. at Ex. 11, p. 1. Dr. Thomas Gulick wrote that her study was abnormal in the upper extremities. Med. recs. at Ex. 11, p. 2. The nerve conduction study showed marked prolongation of the left median nerve distal motor latency at the left wrist with unobtainable left median nerve sensory response. This could be consistent with left carpal tunnel syndrome. The remainder of the EMG/NCV study of the upper extremities was normal. *Id.*

On July 3, 2000, petitioner saw Dr. John J. Ferrell, an orthopedic surgeon. Med. recs. at Ex. 13, p. 308. In May 1998, petitioner had her second hepatitis B vaccination and, in late May or June, developed a febrile illness with swollen joints, skin rash, and elevated white count. *Id.* Dr. Ferrell's impression was serum sickness vs. rheumatoid arthritis with resulting mid-carpal collapse consistent with RA. Med. recs. at Ex. 13, p. 307.

TESTIMONY

Dr. Yehuda Shoenfeld testified for petitioner. Tr. at 5. He is the head of the Department of Medicine at the Sheba Medical Center in Tel Aviv and heads the Center for Autoimmune Diseases. Tr. at 5, 7. He has written over 1,200 medical articles published in peer-reviewed journals as well as 130 book chapters and 43 books. Tr. at 7. He is on 36 editorial boards. *Id.* Dr. Shoenfeld is the editor of *Autoimmunity Review* and of the *Israel Journal of Medical Sciences* and co-editor of the *Journal of Autoimmunity*. Tr. at 7, 8. He is a member of the

[3] Arthropathy is "any joint disease." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 156.

American College of Rheumatology and the European League for Rheumatology. Tr. at 9. Rheumatology is incorporated into the Center for Autoimmune Diseases which he heads. Tr. at 10.

Dr. Shoenfeld testified that almost all rheumatological diseases are autoimmune. *Id.* He predicts that a future medical specialty will be called autoimmunology, comprising rheumatology, neurology, and ophthalmology. *Id.* He stated all autoimmune diseases have a common mechanism and the same therapies. Tr. at 11.

Regarding petitioner, Dr. Shoenfeld testified that she did not have serum sickness. Tr. at 12. Serum sickness is an acute reaction to the serum of another species and involves the humoral component of the immune system. *Id.* This consists of immunoglobulins which bind specifically to the foreign substance and cause inflammation by the area of the Y-shaped immunoglobulins which then activate another set of proteins in the serum called the complement which mediates and causes the inflammation. Tr. at 13. The most frequently measured complement components are C3 and C4. Tr. at 14. In petitioner's case, the complement components were measured and were at increased levels rather than being reduced which would mean complement consumption. *Id.* These elevated complement component levels contradict a diagnosis of serum sickness in petitioner. *Id.*

Another reason for Dr. Shoenfeld's opinion that petitioner did not have serum sickness following vaccination is that the symptoms of serum sickness are acute, but petitioner's symptoms lasted weeks, months, and even years. Tr. at 14-15. His last reason for denying petitioner had serum sickness after vaccination is that there is no serum in the vaccine. Tr. at 15.

In the last 20 years, Dr. Shoenfeld has not seen even one case of serum sickness in his hospital. *Id.* Although petitioner's treating physicians raised the possibility of serum sickness as part of their differential diagnosis, that was only when she was in an acute phase. Later on, they would not have raised it. Tr. at 16.

Regarding whether petitioner had strep throat, Dr. Shoenfeld testified that she did not. Tr. at 17. There was a note in the medical records about beta strep. *Id.* When someone encounters a bacterial infection, one classic symptom is fever. Tr. at 18. Bacteria release lipopolysaccharide into the blood, causing the fever. *Id.* There are two kinds of immune systems, one innate and the other acquired. *Id.* The innate immune system consists of white blood cells classified by subtype. *Id.* The most important of the white blood cells are the polymorphonuclei which are the first combat soldiers against bacterial infections. *Id.* The immune system increases the white blood cells by recruitment of younger white blood cells. This process is called called leukocytosis which results in over 10,000 white blood cells. Tr. at 19. This is called a shift to the left. *Id.* A leukemoid reaction would be over 30,000 white blood cells. Tr. at 21. We do not see leukemoid reaction in strep infection. *Id.* Yet, petitioner had 33,000 white blood cells. Tr. at 22.

Once someone has leukocytosis, the infection can subside naturally because of our immune response or by assistance through antibiotics. *Id.* Petitioner had antibiotics. *Id.* One of the antibiotics she received was Cephalosporin to which strep infections are extremely sensitive. Tr. at 22-23. The next day after taking Cephalosporin, the fever will decrease and the number of leukocytes return to normal. Tr. at 23. But petitioner's fever and her leukocytosis continued for several months. *Id.* Thus, Dr. Shoenfeld stated that petitioner did not have a strep infection or

serum sickness. Tr. at 24. If she had a strep infection, it was insignificant (after serological markers were done, an antistreptolysin titer was in her file). *Id.* Antistreptolysin titer can be found in everyone's blood because all of us are exposed to strep all the time. *Id.* It does not mean someone has a current infection. *Id.* The way to diagnose strep infection or pharyngitis is to culture and grow it. Tr. at 25.

Dr. Shoenfeld said petitioner had fever that was subfebrile, not severe. *Id.* This continued for a long time. Tr. at 26. Infection, however, is defined by acuity. *Id.* Petitioner also had high white blood cells (leukemoid reaction) associated with joint pains (arthralgia). *Id.* These joints pains evolved to swelling, redness, some doctors described synovitis (inflammation of the lining of the joints), and arthritis. Tr. at 27. She had morning stiffness, which is characteristic of rheumatoid arthritis. Tr. at 27-28. Joint pains are usually not characteristic of strep B infection unless someone had rheumatic fever, which petitioner did not. Tr. at 28. Petitioner had an increased alkaline phosphatase, a liver function test, which remained high throughout her follow-ups, which is not consistent with pharyngitis. Tr. at 29.

Dr. Shoenfeld diagnosed petitioner with an autoinflammatory reaction to hepatitis B vaccine she received one month earlier, which was characterized by a low-grade fever that is very common in autoinflammatory reactions and which he called inflammation fever. Tr. at 30. Secondly, petitioner had joint pains starting as arthralgia that continued as arthritis typified by morning stiffness and disability. Thirdly, she had increased inflammatory markers. *Id.*

Dr. Shoenfeld discussed in detail petitioner's inflammatory markers. She had an extremely high sedimentation rate of over 100. High sedimentation rates can be seen in serum sickness but they do not reach over 100. *Id.* Petitioner's high sedimentation rate raised the

differential diagnosis of all the autoimmune rheumatic conditions: rheumatic arthritis, systemic lupus erythematosus, mixed connective tissue disease, polyarteritis nodosa, and temporal arthritis. Tr. at 30-31. Dr. Shoenfeld has written several articles on the significance of the sedimentation rate test. Tr. at 31.

Petitioner's C-reactive protein (CRP) was also quite high. Tr. at 31-32. This also indicatesd continuous activity of the autoinflammation. Tr. at 32. She developed an antinuclear antibody (ANA) of 1:40 and then 1:80 of a speckled pattern. Tr. at 32-33. This may also indicate an autoimmune rheumatic disease. Tr. at 33. She also eventually developed peripheral neuropathy which electromyography helped to diagnose. *Id.*

Dr. Shoenfeld analyzed this case as follows: petitioner received her third hepatitis B vaccination and, one month later, developed continuous fever, joint pains, high markers of inflammation (ESR and CRP), a waxing and waning rash (typical for many autoimmune rheumatic diseases), non-specific markers of an autoimmune rheumatic condition, and peripheral neuropathy. Tr. at 33-34. The vaccine was most probably the trigger mechanism added onto her genetic propensity. Tr. at 34. He specifically blamed the adjuvant in the vaccine whose purpose is to enhance the immune reaction but, in this case, overstimulated it. *Id.*

Dr. Shoenfeld's first diagnosis for petitioner's condition was nonspecific arthritis. This is an undefined connective tissue disease. Tr. at 35. Petitioner had four out of 11 criteria to fulfill the diagnosis of systemic lupus erythematosus (SLE). Tr. at 35-36. These are polyarthritis, elevated ANA, rash, and neurologic involvement. Tr. at 36. But since petitioner did not have classic SLE, she might be said to have a SLE-like disease. *Id.*

In the alternative, petitioner could have seronegative rheumatoid arthritis because she did not have a positive rheumatoid factor. *Id.* But Dr. Shoenfeld preferred the diagnosis of undifferentiated connective tissue disease or polyarthritis. Tr. at 37. This is a rheumatological disease. *Id.* Most probably the cause is an accumulation from the stimulus caused by all three vaccinations. Tr. at 38, 40. Women more frequently have autoimmune diseases than men do because their immune systems are stronger. Tr. at 41, 42. Petitioner received her first hepatitis B vaccination while two weeks pregnant and pregnancy is when a woman's immune system responds most strongly. Tr. at 42.

In explaining the medical theory connecting hepatitis B vaccine to petitioner's nonspecific arthritis, Dr. Shoenfeld discussed molecular mimicry during which the body reacts against a foreign substance in the vaccine which mimics one of the body's own components and then attacks those components as well. Tr. at 43-44. One of the components in hepatitis B vaccine has been identified: the enzyme polymerase. Tr. at 44. Combined with the adjuvant, it stimulates the immune response. Tr. at 45. A third theory is epitope spreading which occurs when the immune system develops autoantibodies or antibodies toward a part of a molecule. *Id.* An epitope is an antigenic determinant. Tr. at 46. In multiple sclerosis, there has been immunization of mice with one epitope of myelin basic protein, causing the mice to develop antibodies against another epitope on the myelin basic protein, with the mice eventually developing experimental allergic encephalomyelitis (EAE). Tr. at 47.

Dr. Shoenfeld testified there was a logical sequence of cause and effect between hepatitis B vaccine and petitioner's injury because of autoimmunity. Tr. at 54. Petitioner had the genetic background to develop autoimmunity. *Id.* She has some defect in her immune system and a

trigger mechanism in the environment. *Id.* Dr. Shoenfeld could not find any other mechanism one month before her disease onset except the vaccine. *Id.* The vaccine is known to induce polyarthritis. Tr. at 55.

Dr. Shoenfeld testified that the temporal association in this case was optimal, the most optimal or classic that he has seen, between the insulting agent and the start of the autoimmune disease. Tr. at 57.

On cross-examination, Dr. Shoenfeld stated there were several papers linking hepatitis B vaccine and inflammation of the joints. Tr. at 58. He mentioned references 40 (Maillefert), 41 (Pope), 42 (Gross), 43 (Bioli), 44 (Biasi), and 45 (Hachulla). Tr. at 59. The timing between stimulus and onset was usually about one months, or two to three months. Tr. at 60.

Dr. Alan Brenner testified for respondent. Tr. at 62. He is chief of rheumatology at a medical group in Massachusetts and heads another rheumatology department at a local medical center. He is board-certified in internal medicine and rheumatology. Tr. at 63. His opinion is that hepatitis B vaccine did not cause petitioner's rheumatic problem. Tr. at 65. The first basis of his opinion is that, other than for case reports and small case series, there is no documented medical literature associating hepatitis B vaccine with rheumatoid arthritis. *Id.* Secondly, other than in serious chronic viral hepatitis, there is no evidence of hepatitis B virus causing arthritis. *Id.* Thirdly, if there were causation, the appropriate timing for the onset of arthritis would be 10 to 14 days post-vaccination, not one month. *Id.* Fourthly, an interceding event, i.e., streptococcal pharyngitis defined by a positive beta strep cultured and an elevated ASO (antistreptolysin O) is the cause of petitioner's rheumatoid arthritis. Tr. at 65, 66.

Dr. Brenner is not sure that petitioner ever had an active objective arthritis. Tr. at 67. He knows she had a lot of joint symptoms, fever, and a macular rash. *Id.* These symptoms occurred closer in time to the strep infection than to the hepatitis B vaccination. *Id.* Dr. Brenner mentioned another entity distinct from streptococcal sepsis, called poststreptococcal reactive arthritis which causes diffuse inflammation and acute rheumatic fever causing joint symptoms, rash, fever, and usually heart damage or neurologic symptoms. *Id.* It begins almost immediately or within a few days of an antecedent strep infection. Tr. at 68.

Dr. Brenner thinks that petitioner had an immune reaction to the strep infection, causing fever, rash, and articular symptoms. Tr. at 69. He does not think petitioner's fever started until she developed pharyngitis and was related to it. Tr. at 70, 72. Petitioner was on corticosteroids which have the effect of raising the white blood count. Tr. at 72. He agreed with Dr. Shoenfeld that petitioner had a leukemoid reaction, which is seen predominantly in certain kinds of infection, but not viral infections. *Id.* Dr. Brenner could not see why hepatitis B vaccine would cause a leukemoid reaction if the hepatitis B virus itself did not. Tr. at 73. Dr. Brenner said he did not know what the significance of petitioner's greatly elevated white blood count was and had been struggling with that question. *Id.* However, he does know that the elevated white blood count is inconsistent with a viral infection and with adverse reactions to vaccination. Tr. at 73-74. It is also inconsistent with an autoimmune condition like systemic lupus erythematosus. Tr. at 74.

Dr. Brenner stated he does not know what an autoinflammatory reaction is. *Id.* He stated petitioner was consistently hepatitis B antibody negative and therefore a non-responder to the vaccine. *Id.* Dr. Brenner said that if she did not generate antibodies to the vaccine, it would be

tough for her to have an antigen-antibody reaction. *Id.* He testified it would be difficult to define her condition as autoinflammatory with no autoimmune markers other than the development of a low titer ANA later on. Tr. at 74-75. This confirms his opinion that hepatitis B vaccine had no role in causing petitioner's disease. Tr. at 75.

Dr. Brenner disagreed with Dr. Shoenfeld's statement that the literature associates hepatitis B infection with inflammatory and destructive involvement of the joints. *Id.* One of the reports Dr. Shoenfeld mentioned in his expert report refers to a patient who had osteoarthritis of the knee with multiple steroid injections into the joint who then had an overwhelming hepatitis B infection so that doctors found hepatitis B virus in his joint tissue. Dr. Brenner said this had nothing to do with petitioner's case. *Id.* Dr. Brenner is aware of medical literature associating hepatitis B vaccine with inflammation of the joints, but not destruction of the joints. Tr. at 75-76. These are all individual case reports or very small series. Tr. at 76.

Dr. Brenner testified that a paper by Al Kheim showed that hepatitis B vaccine did not exacerbate rheumatoid arthritis in patients who already had the disease. *Id.* Dr. Brenner stated that Maillefert and Sibilia who wrote the original arthritis article which Dr. Shoenfeld cited wrote an editorial on Al Kheim's article saying maybe in light of there being no exacerbation of rheumatoid arthritis with hepatitis B vaccine, there might be no association between rheumatoid arthritis and hepatitis B vaccine. *Id.* There are also articles denying an association between hepatitis B vaccine and systemic lupus, and hepatitis B vaccine and multiple sclerosis as well as exacerbation of multiple sclerosis. Tr. at 76-77.

Dr. Brenner disagreed with the timing of one month between vaccination and onset of disease as being appropriate, saying the average time frame was 10 to 14 days. Tr. at 77. He also

disagreed that the vaccine adjuvant, aluminum hydroxide, had any effect on petitioner since she did not mount a humoral response. Tr. at 78. He denied that petitioner's having received her first hepatitis B vaccine while pregnant would have enhanced a later reaction to her other vaccinations. *Id.* Hepatitis B vaccine is a weak antigen. Tr. at 79. That is why three doses of it are given. *Id.* Since it is a weak antigen, it is a weak reactigen. *Id.*

Dr. Brenner testified that the three theories Dr. Schoenfeld described (molecular mimicry, adjuvant, and epitope spreading) are the common theories of how vaccination and other stimuli may lead to autoimmune conditions. Tr. at 79-80. The only case of molecular mimicry of which Dr. Brenner is aware is the development of Lyme arthritis from Lyme vaccine. Tr. at 80. Strep infection in acute rheumatic fever is probably another example of molecular mimicry because it mimics a molecule in cardiac tissue, but he would not apply that to vaccines. *Id.* Dr. Brenner said he had read about these theories a million times and had read all of Dr. Shoenfeld's literature. *Id.*

Dr. Brenner testified that he did not think there was a logical sequence of cause and effect between hepatitis B vaccine and petitioner's symptoms. Tr. at 81. He stated that we know that various forms of arthritic problems are based on different issues of immunogenetics and that, generally, if we look at rheumatoid arthritis, certain stimuli are more likely to cause it than other stimuli. *Id.* The stimulus of reactive arthritis is bacterial, which has always puzzled Dr. Brenner. *Id.* He asked how one little hepatitis B subparticle could cause conditions that are so disparate in immunogenetics as rheumatoid arthritis. Tr. at 81-82. He did not know of any other example in nature where it does. Tr. at 82.

Dr. Brenner testified that even if he accepted Dr. Shoenfeld's three theories of causation, there was no evidence that they occurred here because petitioner had no immune response to hepatitis B vaccine. *Id.* Dr. Brenner defined post-streptococcal reactive arthritis as a particular form of immune inflammatory process associated with beta strep infection. Tr. at 83. It is a symmetrical small- and large-joint arthritis which can be associated with an evanescent macular nonpalpable or slightly palpable rash. *Id.* It is definitely associated with fever which lasts a long time and is very difficult to treat. *Id.* He thinks petitioner's doctors missed her diagnosis. *Id.* He thinks more likely than not that petitioner's illness was strep-related and not hepatitis B vaccine-related. Tr. at 84-85. He did not think that hepatitis B vaccine was a trigger. Tr. at 85. He also did not think that the development of a low-titer ANA later had any specificity or significance. Tr. at 86. All of petitioner's lupus antibodies were negative. Tr. at 87.

Dr. Brenner agrees with Dr. Shoenfeld that petitioner has nonspecific arthritis or polyarthritis, undifferentiated arthritis. Tr. at 88. However, he thinks that her objective joint inflammation resolved and she developed a chronic pain syndrome that is not definable as a chronic persistent arthritis. *Id.* Then, petitioner was referred to chronic pain managers. *Id.* About 10 of Dr. Brenner's 20 daily patients have autoimmune disorders. *Id.* Dr. Brenner stated that post-strep reactive arthritis is different than all the other postinfectious reactions immunogenetically. It is not an autoantibody reaction. Tr. at 94. It can occur immediately with the sore throat. *Id.*

Dr. Brenner did not think that an onset of strep reactive arthritis simultaneously with petitioner's sore throat was difficult to explain immunologically. Tr. at 96. Petitioner had the strep in her system before she was symptomatic with pharyngitis. *Id.* The literature on

poststreptococcal reactive arthritis says it can take a few days to develop or develop simultaneously. *Id.*

Dr. Brenner admitted that the medical literature shows an onset of arthritis one month after hepatitis B vaccination. Tr. at 97. He has seen the literature showing positive rechallenge for reactive arthritis and rheumatoid arthritis after hepatitis B vaccination. Tr. at 98-99. He agreed that positive rechallenge was strong evidence of causation when someone proves the patient mounted an immune response to the first and second vaccinations, but in this case, no one can prove that. Tr. at 99. However, he disagreed that positive rechallenge proved causation. *Id.* Dr. Brenner stated he respected Dr. Shoenfeld a lot. Tr. at 101.

The Maillefert article discussed a case that occurred more than a month post-vaccination. *Id.* He has never faced this issue clinically so it is difficult for him to know about causation from the hepatitis B vaccine. Tr. at 102. Dr. Brenner thinks that because petitioner did not mount an immune response to the hepatitis B vaccine, she could not have had an autoimmune reaction. *Id.* He admitted that there are case reports and small case series reporting the possible development of rheumatoid arthritis 10 to 14 days after hepatitis B vaccination. Tr. at 104.

Dr. Brenner said he has seen about 10 cases of poststrep reactive arthritis. Tr. at 105. The literature he intended to submit after trial showed onset of poststrep reactive arthritis five to seven days after the onset of the sore throat. Tr. at 110.

Dr. Shoenfeld resumed testifying, stating that he had seen many patients with Still's disease[4] but rarely someone with poststreptococcal infective arthritis or reactive arthritis with

[4] Still's disease is "a variety of chronic polyarthritis affecting children and marked by enlargement of lymph nodes, generally of the spleen, with evanescent rash and irregular fever; see also *juvenile rheumatoid arthritis*." Dorland's Illustrated Medical Dictionary, 30th ed. (2003)

accumulating disease and disability. Tr. at 114. He discussed two mechanisms by which streptococcus could cause arthritis. The first is that the infecting agent invades the joint. *Id.* But if someone receives antibiotics, and petitioner did receive them (Ampicillin and Cephalosporin) in this case, she would have recovered completely. *Id.* Here petitioner had a year's prolongation of disease with aggravation of it leading to complete disability. Tr. at 115. Thus, Dr. Shoenfeld doubted that petitioner had a poststreptococcal arthritis appearing together with pharyngitis and arthritis. *Id.* The second mechanism might be Still's Disease, which petitioner might have. *Id.* One of the main reasons for his opinion is petitioner's leukemoid reaction. *Id.* Petitioner had very high levels of white blood cells and joint pain, which are symptoms of a variant of rheumatic arthritis at an early age called Still's disease. She also had rash. *Id.* She had spiking fever and not all Still's disease cases are characterized by continuous spiking fever. Tr. at 116. Lastly, she had liver function derangement, which is classic for Still's disease. *Id.*

Dr. Shoenfeld then explained leukocytosis. There is an inflammatory reaction of at least two cytokines: IL-1 and IL-6. *Id.* These are the most important inflammatory cytokines known to cause leukocytosis and inflammation of the joint. *Id.* "IL" stands for interleukin. Tr. at 117. In rheumatic fever, streptococcus, which harbors a special epitope called M protein, invades the pharynx and, only after 21 days, and sometimes after 30 days, the patient develops autoantibodies directed against the M protein. Tr. at 118. This does not happen after seven, 10 or 14 days. *Id.* These antibodies attack the brain, joints, and heart because they all harbor M protein. *Id.* By analogy, vaccine can cause autoimmune disease classically after three or four weeks because it takes the immune system at least that time to produce immunoglobulin. *Id.* Sometimes after a

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at 542.

second or third challenge, the exacerbation may occur earlier, but the first attack appears usually after months or more. Tr. at 119-19.

Dr. Shoenfeld concluded that he disagreed with the idea of a poststreptococccal infection not responding to an antibiotic, causing a disease which is not typical of postreptococcal arthritis, including the prolonged follow-up, and also the development of neuropathy which may be part of an autoimmune reaction but definitely is not part of poststreptococcal disease. Tr. at 119-20. Peripheral neuropathy may be part of Still's disease because Still's is systemic while reactive arthritis is organ-specific, i.e., specific to the joints. Tr. at 120. In all the autoimmune rheumatic diseases, we have other systemic manifestations in what is called a cytokine storm. *Id.* In rheumatoid arthritis, we have pericardial, lung, and blood involvement. *Id.*

Dr. Shoenfeld responded to Dr. Brenner's point that, since petitioner's titers to hepatitis B surface antigen were negative, Dr. Brenner said she could not have had an abnormal reaction to the vaccine and therefore hepatitis B vaccine did not cause her arthritis. Tr. at 121. Dr. Shoenfeld testified that the immune system may have different deviations and may react to one component of the vaccine and not another. *Id.* Dr. Shoenfeld added a fourth mechanism for the reaction, which is polyclonal activation. Tr. at 122. The vaccine adjuvant nonspecifically stimulates the immune system to generate many immunoglobulins, among which one causes the arthritis or the eventual development of antinuclear antibodies. *Id.* In polyclonal activation, the mechanism may cause the disease, but the patient may be deficient in developing antibodies to the specific viral ingredient in the vaccine. Tr. at 123. Not reacting to the viral ingredient in the vaccine does not prevent the immune system from adjuvant stimulation and generation of autoantibodies or autoreactive agents. *Id.*

Dr. Brenner also mentioned petitioner's mild regurgitation of blood in her heart detected on echocardiography, indicating a heart problem. *Id.* Dr. Shoenfeld identified this as a mild mitral insufficiency which is insignificant. Tr. at 124. There was never a detection of a heart murmur. *Id.* In many examinations, her heart was noted to be unremarkable. *Id.* Petitioner's mild mitral insufficiency never progressed as it would with rheumatic fever, the other disease that streptococcal infection causes. Tr. at 126.

In petitioner's case, the medical treaters did not culture out her strep. Tr. at 127. This is why her doctors, except for Dr. Anders, did not diagnose her with pharyngitis. *Id.* Dr. Shoenfeld believed that petitioner's strep infection was insignificant and intercurrent with her severe disease that she developed later. Tr. at 128. Petitioner's developing an autoimmune response did not make her more vulnerable to a strep infection. *Id.* Patients with autoimmune diseases do not have more infections except following therapy with immunosuppressive drugs. *Id.* Petitioner's leukocytosis was an inflammatory reaction to the cytokine storm she had after reacting to the vaccine trigger and not to the streptococcal infection. Tr. at 129. Streptococcal infection never causes leukocytosis of 33,000 lasting several months. *Id.* Dr. Shoenfeld believes petitioner suffers from Still's disease. *Id.*

Dr. Shoenfeld said that no one could say what is petitioner's definite diagnosis. Tr. at 130. He posited reactive polyarthritis, seronegative rheumatoid arthritis, and Still's disease. *Id.* All of them are encompassed within an autoinflammatory reaction. Tr. at 131. Many patients with autoimmune disease do not fall within strict categories. *Id.* There is no other factor than the vaccine to which to ascribe petitioner's autoinflammatory reaction. *Id.* Although petitioner was 33 years old when she got sick, she still falls within the category of juvenile arthritis (Still's

disease is more common in young people). Tr. at 132. All these arthritides have in common leukocytosis, fever, and biological inflammatory markers, such as C-reactive protein (CRP) and elevated sedimentation rate (ESR). Tr. at 132-33.

Dr. Brenner resumed testifying at this point in response to Dr. Shoenfeld's testimony. Tr. at 134. He stated that poststreptococcal reactive arthritis is not responsive to antibiotics. Tr. at 135. The fact that petitioner's condition did not respond to antibiotics does not mean it was not poststreptococcal. Tr. at 136. Petitioner had a throat culture positive for some beta strep although the group had not been reported. Dr. Brenner questioned whether it was a strep infection. Tr. at 137.

As to petitioner's developing a neuropathy after her arthritis, Dr. Brenner stated that the only manifestation of neuropathy petitioner had was carpal tunnel syndrome which can have a million causes. Tr. at 138. He disagreed with Dr. Shoenfeld's diagnosis of Still's disease because petitioner's fever history did not fit the Still's disease pattern. Tr. at 140. She had a persistent low grade fever around 100º at the hospital, not the kind of temperature curve with a daily spike returning to normal daily or twice daily as she would have had if she had Still's disease. Dr. Brenner did not think petitioner's rash was typical for a Still's disease rash. *Id.* She did not have any of the other manifestations of Still's disease, such as adenopathy, and liver and spleen enlargement. *Id.*

Dr. Brenner disagreed with Dr. Shoenfeld's opinion that reactive polyarthritis, seronegative rheumatoid arthritis, and Still's disease are roughly the same. Tr. at 141. His reason is that reactive polyarthritis assumes a reaction to an infectious agent, usually bacterial, whereas seronegative rheumatoid arthritis assumes a course of erosive small- or large-joint

polyarthritis that happens to be seronegative. *Id.* Still's disease is one form of juvenile chronic polyarthritis. There is also an adult Still's disease. Tr. at 142. Still's disease very commonly responds to anti-inflammatories. *Id.* Petitioner was treated with anti-inflammatories and responded poorly just as patients with poststreptococcal reactive arthritis respond in the literature. Tr. at 143. Dr. Brenner does not believe petitioner has Still's disease. *Id.* He thinks petitioner has something roughly like Still's disease if one included reactive polyarthritis and seronegative rheumatoid arthritis although he thought it a stretch. *Id.*

Dr. Brenner thinks there was no accepted timing interval here between vaccination and arthritis. Tr. at 145. He does not know why a reaction would have taken as long as a month. *Id.* Petitioner has mitral valve prolapse and Dr. Brenner said that a heart murmur is the most common cardiac abnormality associated with poststreptococcal reactive arthritis. Tr. at 146.

Dr. Shoenfeld then responded to Dr. Brenner's testimony. Tr. at 147. Dr. LaRocco's assessment that petitioner had a culture positive for beta strep infection was a mistake. Dr. LaRocco was referring to the antistreptolysin titer and not to the culture, according to Dr. Shoenfeld. *Id.* There was no culture done and therefore no streptococci grown. *Id.* Dr. LaRocco included a differential diagnosis of parvovirus infection and mycoplasma in his assessment. Tr. at 147-48. Dr. Shoenfeld asked why would Dr. LaRocco raise alternate diagnoses of parvovirus or mycoplasma if there had been a positive streptococcal culture? Tr. at 148.

Regarding petitioner's having just carpal tunnel syndrome rather than a true neuropathy, Dr. Shoenfeld stated that petitioner was too young for just idiopathic carpal tunnel syndrome.

Carpal tunnel syndrome is part of the rheumatic manifestation and belongs in the category of neuropathy. *Id.*

As for timing, Dr. Shoenfeld stated that immunological reactions take about three weeks. Tr. at 149. The production of immunoglobulin takes three weeks. Tr. at 150.

Dr. Brenner answered the question about timing in the context of this occurring after petitioner's third vaccination. Tr. at 151. There is no evidence of an antibody immune response here. *Id.* Petitioner did not have an antibody response to hepatitis B. *Id.* She did not have an excess of gamma globulin even when she was at her sickest in the hospital. *Id.* She did not have a reaction to anything but strep. Tr. at 152.

Dr. Shoenfeld admitted that petitioner had an antibody to strep (ASO) of the IgG isotope. But all this test result indicated was her exposure in the past to streptococcus. *Id.* Dr. Brenner said the optimum is to obtain an ASO titer and, if it is elevated, repeat it in two or three weeks to answer whether this was an underlying response or an acute response to a repeat infection. Tr. at 153. There is no evidence here of a cellular immune response, but no one looked for it. Tr. at 154. Dr. Shoenfeld said that petitioner had an invasion of her joints with autoreactive lymphocytes. Most arthritides are classified as cellular autoimmune reactions. Tr. at 155. Dr. Brenner said the record does not indicate any immune response. *Id.*

Dr. Shoenfeld disagreed that there was no evidence of any immune response because of petitioner's elevated C-reactive protein and sedimentation rate, and her leukocytosis. Tr. at 156. In order to get evidence of a cellular invasion of her joints, one would have to do a biopsy. *Id.* But the representation of this invasion was her chronic joint pains. The arthritis is the evidence of her immune response. *Id.* Even accepting Dr. Brenner's thesis of her arthritis being secondary

to streptococcus makes this an immune response because streptococcus was not in her joints. Tr. at 156-57.

Dr. Brenner stated that he did not need to find streptococcus in petitioner's joints to determine that petitioner had an immune response to the strep. Tr. at 157. He has no argument with Dr. Shoenfeld's stress on petitioner's leukocytosis, elevated sedimentation rate, and elevated CRP, but they are nonspecific markers of any inflammation. *Id.*

Dr. Brenner admitted that the two sides in the case disagree only about to what stimulus petitioner was reacting: hepatitis B vaccine or streptococcus. They both agree that she had an immune response. Tr. at 158.

Other Submitted Material

Petitioner filed 45 medical articles (exhibits 26-70). Respondent filed 13 medical articles (exhibit C, tabs 1-13).

Petitioner's Ex. 26, an article entitled "BCG immunisation and the 'Trojan Horse' phenomenon of vaccination" is co-written by petitioner's expert Dr. Shoenfeld. (The other author is A. Aron-Maor and it is published in 22 *Clin Rheumatol* 6-7 (2003). The authors state that hepatitis B vaccine is the vaccine most often involved with autoimmunity, having been connected to systemic lupus erythematosus, rheumatoid arthritis, and non-specific autoimmune manifestations. *Id.* at 6. Three of the citations to this statement include two references that the authors wrote and one reference they did not write which is P. Ex. 66, "Vaccination and rheumatoid arthritis" by J. Sibilia and J.F. Maillefert, which was downloaded from the *Br Med J* 575-76 (Sept. 19, 2006).

Petitioner's Ex. 28 is a letter to the editor entitled "A new case of reactive arthritis after hepatitis B vaccination" by D. Biasi, et al., 11 *Clin & Experimental Rheumat* 215-20 (1993). The authors describe a man who developed reactive arthritis two weeks after his second recombinant hepatitis B vaccination. He presented with increasing pain, swelling, joint irritation, lumbar and cervical pain, malaise, and a low-grade fever. He had elevated C-reactive protein and erythrocyte sedimentation rate. *Id.* at 215. The authors conclude that natural hepatitis B virus infection is known to induce arthritis. They found it "conceivable that injected viral antigens in a genetically predisposed subject may have triggered this reactive arthritis." *Id.*

Petitioner's Ex. 32 is a case report entitled "Arthritis after Hepatitis B Vaccination. Report of three Cases" by K. Gross, et al., 14 *Scand J Rheumatol* 50-52 (1995). They discuss three cases of vaccination-induced arthritis, two of them reactive arthritis and the third rheumatoid arthritis. *Id.* at 50. In the first case, a woman experienced symptoms of urticaria (hives) and joint pain two weeks post-vaccination. In the second case, a girl experienced severe pain, swelling, redness, and warmth in her knees beginning one week post-vaccination. *Id.* at 51. In the third case, a woman experienced wrist pain four days post-vaccination. *Id.* Her symptoms resolved but, six months later, after another hepatitis vaccination, her symptoms returned with more severe swelling and pain. *Id.* The authors posited various medical theories to explain these reactions. One was circulating immune complexes. *Id.* Another was molecular mimicry. *Id.* at 52.

Petitioner's Ex. 33 is a letter to the editor entitled "Reactive Arthritis After Hepatitis B Vaccination" by E. Hachulla, et al., 17 *J Rheumatol* 1250-51 (1990). A 19-year-old healthy man developed reactive arthritis two weeks after receiving a combination of salmonella and hepatitis

B vaccine (Hevac B).[5] He had a second attack two weeks after receiving a second salmonella and hepatitis B vaccine. *Id.* at 1251. He had no fever and no recent infection. Tests for rheumatoid factor and antinuclear antibodies were negative. HLA-B27 antigen was found. *Id.* The authors conclude:

> It is conceivable that the host's immune response to a variety of newly presented antigens, due to infection or vaccination, can be important in the pathogenicity of reactive arthritis in HLA-B27 positive patients. The role of circulating immune complexes can be suggested. . . . The association between HLA antigens and susceptibility to reactive arthritis may also be explained in 2 ways: (1) the antigen present in hepatitis B virus vaccine interacts with HLA-B27 antigens on lymphocytic membranes . . . and alters its normal physiological function, (2) cross reacting antigenic determinants may exist between some infectious antigens and HLA-B27 antigen. Recurrent arthropathy in reactive arthritis is well recognized, and the second vaccination with hepatitis B may have been coincidental. Nevertheless, the short interval between vaccination and arthritis after the first and the second injection of Hevac B suggests a relationship of cause and effect.

Id.

Petitioner's Ex. 34 is an article dealing with hepatitis virus, not hepatitis vaccine, entitled "Rheumatic Manifestations of Hepatitis B Virus Infection," by R.D. Inman, 11 *Seminars in Arthritis and Rheumatism* 4:406-20 (1982). The author states, "Reports on the coincidence of arthritis and hepatitis date back to the early 19th century, and data on the frequency of this association have varied." *Id.* at 407. He states, "The arthritis associated with acute hepatitis type B may be mediated by immune complexes. Complement consumption data support this." *Id.* at 409.

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[5] The hepatitis B vaccine at issue in the instant action is recombinant vaccine containing hepatitis B surface antigen, not plasma vaccine containing hepatitis B surface antigen (Hevac B) as described in the letter that is Ex. 33 at 1251.

Petitioner's Ex. 36 is an article entitled "Rheumatic disorders developed after hepatitis B vaccination" by J.F. Maillefert, et al., 38 *Rheumatology* 978-83 (1999). Out of 22 patients, the authors found five had post-vaccinal arthritis. All the patients received recombinant vaccine. *Id.* at 979. In three of these cases, after another vaccination was administered, all three had a worsening of complaints. *Id.* The authors state:

> Several pathogenetic models can be put forward to explain rheumatic disorders following hepatitis B vaccination. Transient conditions might be due to deposition within the synovium of circulating immune complexes containing viral antigen and anti-HBs antibodies, such as observed is some hepatitis B infections . . . . Onset of chronic inflammatory or autoimmune diseases might be due to molecular mimicry or to post-immunization conditions indistinguishable from individualized diseases. . . . A more attractive hypothesis is that hepatitis B immunization might trigger the onset or the relapse of the diseases in individuals with underlying genetic and immunological susceptibility.

Id. at 981-82.

They continue:

> For a majority of patients, the temporal association was suggestive. The manifestations worsened in most of the patients who were given a further injection. . . . In most patients, the explorations and the follow-up did not show any other plausible cause for the complaints.

Id. at 982.

They conclude that "hepatitis B vaccine might be followed by various rheumatic conditions and might trigger the onset of underlying inflammatory or autoimmune rheumatic diseases" and suggest conducting epidemiological studies to establish causation. *Id.*

Petitioner's Ex. 37 is an article entitled "Infection, vaccines and other environmental triggers of autoimmunity" by V. Molina & Y. Shoenfeld (petitioner's expert herein), 38

Autoimmunity 3:235-45 (2005). The authors state that the etiology of autoimmune diseases is not clear "but genetic, immunological, hormonal and environmental factors are considered to be important triggers." *Id.* at 235. They state that clinical symptoms do not occur in the context of autoimmunity "unless an additional event such as an environmental factor favors an overt expression." *Id.* They state that one of those environmental factors can be vaccinations: "The same mechanisms that act in infectious invasion of the host apply equally to the host response to vaccination." *Id.* at 239. They continue:

> The occurrence of arthritis has been described following administration of several vaccines and can be divided into *isolated* or *reactive arthritis* (poly or monoarticular) and arthritis as a symptom of a *systemic autoimmune* disease (such as SLE [systemic lupus erythematosus] or RA [rheumatoid arthritis]). (Emphasis in original.)

Id. at 240.

Petitioner's Ex. 39 is an article entitled "The Development of Rheumatoid Arthritis After Recombinant Hepatitis B Vaccination" by J.E. Pope, et al., 25 *J Rheumatol* 1687-93 (1998). The authors note that there have been sporadic reports of inflammatory polyarthritis after vaccination with recombinant hepatitis B vaccine. *Id.* at 1687. They describe a group of 11 previously healthy adults who, after receiving recombinant hepatitis B vaccine, had a persistent and, in some cases, severe form of inflammatory polyarthritis, frequently RA. *Id.* Seven had onset two weeks after their vaccination and one had onset three weeks after vaccination. *Id.* at 1689.

Petitioner's Ex. 40 is an analytical review entitled "Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines" by A. Schattner, 23 *Vaccine* 3876-86 (2005). The author states that although reactive arthritis has

been reported after receipt of recombinant hepatitis B vaccine, he cautioned against linking hepatitis B vaccine and autoimmune manifestations. *Id.* at 3877-78.

Petitioner's Ex. 42 is a chapter entitled "Vaccines and Autoimmunity" by M. Tishler and Y. Shoenfeld (petitioner's expert herein) in the textbook The Autoimmune Diseases, 4th ed., eds. N.R. Rose and I.R. Mackay (2006) at 309-16. The authors state that only a few cases of arthritis following hepatitis B vaccine have been reported. *Id.* at 314.

Respondent's Ex. C-5 is an article entitled "Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis" by O. Elkayam, et al., 61 *Ann Rheum Dis* 623-25 (2002). The authors state that inoculation of rheumatoid arthritis patients with hepatitis B vaccine did not worsen their disease. *Id.* at 624. The authors state: "We are aware of the limitations of this study. If hepatitis B vaccination induces only a low percentage of flares, ... [t]he design of the study might have failed to demonstrate a flare or an adverse effect between the visits." *Id.* at 625.

DISCUSSION

To satisfy her burden of proving causation in fact, petitioner must prove by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. 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[.]"

As for epidemiological support for causation, the Federal Circuit in Knudsen v. Secretary of HHS, 35 F.3d 543, 551 (Fed. Cir. 1994), ruled for petitioners even when epidemiological evidence directly opposed causation from DPT vaccine. The case concerned the cause of a baby's encephalopathy after a vaccination. Respondent provided evidence that more encephalopathies are caused by viruses than by vaccines, convincing the special master to rule against petitioners. But the Federal Circuit thought the epidemiologic evidence should not bar petitioners from prevailing. Even though epidemiological evidence supported respondent's view 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.

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...."

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, supra, at 1149. Mere temporal association is not sufficient to prove causation in fact. *Id.* at 1148.

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).

Petitioner must show not only that but for the vaccine, she would not have had polyarthritis, but also that the vaccine was a substantial factor in bringing about her polyarthritis. 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.

In Capizzano, the Federal Circuit ruled that hepatitis B vaccine caused petitioner's rheumatoid arthritis. Four of petitioner's treating physicians regarded hepatitis B vaccine as the cause. The Federal Circuit emphasized that the special master should give serious consideration to the treating doctors' opinions in arriving at a conclusion. 440 F.3d at 1326.

In Griffin v. Secretary of HHS, No. 99-378V, 2007 WL 4270698 (Fed. Cl. Spec. Mstr. Nov. 19, 2007), the undersigned ruled that hepatitis B vaccine caused petitioner's systemic scleroderma, which is another rheumatological disease.

In the instant action, both expert medical witnesses testified that petitioner had an autoimmune reaction to something. Their opinions differed on what that cause was. Petitioner's expert Dr. Shoenfeld opined that hepatitis B vaccine caused her reaction. Respondent's expert Dr. Brenner opined that streptococcus caused her reaction (post-strep reactive arthritis). Both agreed that petitioner did not have serum sickness.

However, they diverged in understanding the basic physiology of an autoimmune reaction. Dr. Brenner, respondent's expert, confessed ignorance as to what an autoimmune reaction is. He said that a viral infection cannot cause an elevated white blood cell count. And since hepatitis B vaccine is derived from hepatitis B virus, the vaccine could not cause an elevated white blood cell count either. Similarly, since hepatitis B virus does not cause reactive arthritis, except when there is a serious viral infection, Dr. Brenner said that hepatitis B vaccine cannot cause reactive arthritis either. However, his testimony rejecting an autoimmune characterization of petitioner's arthritis preceded his eventual realization that he did believe petitioner had reactive arthritis and that her reaction was to strep and not to hepatitis B vaccine.

Dr. Brenner mistakes the medical theory Dr. Shoenfeld gave to explain how hepatitis B vaccine causes reactive arthritis. Even if the medical literature consists not of epidemiologic studies but case reports, petitioner does not have the burden of proving her case with objective medical literature or epidemiological studies, according to the Federal Circuit in Knudsen and Althen. Something in this recombinant hepatitis B vaccine triggered in a genetically susceptible individual, the petitioner, a response that caused fever, rash, and joint pain which developed into a nonspecific arthritis as well as a neurologic problem. Dr. Shoenfeld, petitioner's expert, was not impressed with proof of petitioner's pharyngitis or strep B infection.

Even though petitioner does not have the burden of showing that medical literature supports her expert's opinion or of showing positive rechallenge (Althen), the literature petitioner filed in this case does support Dr. Shoenfeld's testimony and does show positive rechallenge (i.e., a patient has the same or worse symptoms after successive hepatitis B vaccinations). See, e.g., petitioner's exhibit 36, the Maillefert article, which discusses three individuals whose symptoms worsened after a subsequent hepatitis B vaccination.

What further impresses the undersigned in the instant action is that four of petitioner's treating physicians thought she had reacted to hepatitis B vaccine, an exact parallel to Capizzano. The first is her treating physician Dr. Kerry Anders, who diagnosed her with pharyngitis, yet ascribed her arthritis to serum sickness, not to strep. Both Dr. Shoenfeld and Dr. Brenner in the instant action testified that petitioner did not have serum sickness because hepatitis B vaccine does not contain serum. But the fact that Dr. Anders misunderstood that hepatitis B vaccine does not contain serum from animals does not negate the fact that he thought she had reacted adversely to the vaccination. He thought she had serum sickness because she had been

vaccinated and her symptoms and the timing were appropriate for him to diagnose her with a vaccine reaction.

The second treating doctor who ascribed petitioner's arthritis to hepatitis B vaccine was the rheumatologist Dr. Robert E. Goodman, who diagnosed petitioner with serum sickness and seronegative rheumatoid arthritis. Again, the serum sickness diagnosis is incorrect, but Dr. Goodman, a rheumatologist just as is respondent's expert Dr. Brenner, had no difficulty implicating hepatitis B vaccine as the cause of her seronegative RA. Dr. Shoenfeld gave three possible diagnoses for petitioner: polyarthritis, Still's disease, and seronegative RA. The undersigned does not find it important to distinguish among them, particularly since Dr. Brenner, respondent's expert, finally admitted his opinion was that petitioner had reactive arthritis (but to strep, not to hepatitis B vaccine). As the Federal Circuit stated in Knudsen, 35 F.3d at 549: "The special masters are not 'diagnosing' vaccine-related injuries."

The third treating doctor who ascribed petitioner's arthritis to hepatitis B vaccine was the pain specialist Dr. Ronald L. Ellis, who diagnosed her with serum sickness and allergic arthropathy with multiple joint pain secondary to serum sickness. Dr. Ellis's "allergic" description of petitioner's illness as due to the serum sickness is key here since the serum sickness diagnosis, incorrect though it may be, leads back to the hepatitis B vaccination.

The fourth treating doctor who ascribed petitioner's arthritis to hepatitis B vaccine was the orthopedic surgeon Dr. John J. Ferrell, who wrote a differential diagnosis of serum sickness vs. rheumatoid arthritis.

Just as in Capizzano, four treating physicians, particularly her general treater Dr. Anders who had diagnosed her with pharyngitis, attributed petitioner's joint condition as well as her

other symptoms to hepatitis B vaccine. Their opinions plus the testimony of Dr. Shoenfeld are sufficient to prove petitioner's case.

Petitioner has prevailed in proving that hepatitis B vaccine caused her nonspecific arthritis. She had shown a biologically plausible medical theory. Dr. Shoenfeld described three various theories to explain her reaction. The undersigned does not have to pick one of them. They are all biologically plausible. The Federal Circuit in Knudsen stated petitioner does not have the burden of proving a specific biological mechanism in order to prevail.

Petitioner has shown a logical sequence of cause and effect that hepatitis B vaccine caused her nonspecific arthritis. As Dr. Shoenfeld stated, after rejecting the accuracy of the initial diagnosis of strep because the test result could have indicated exposure at any time in her life, there was no other antigenic stimulus to which to ascribe her arthritis.

And finally, petitioner has shown a medically appropriate time interval between her vaccination and the onset of her symptoms. This interval was so strikingly appropriate that four of her treaters ascribed her condition to the vaccination.

CONCLUSION

Petitioner is entitled to damages. The undersigned will set up a telephonic status conference to discuss how to proceed with damages.

IT IS SO ORDERED.

January 16, 2009
DATE

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