OFFICE OF SPECIAL MASTERS
No. 04-210V
March 31, 2006
For Publication

PATRICIA SCHRUM,	*	
	*	
Petitioner,	*	
	*	
v.	*	Entitlement; hepatitis B vaccine;
	*	Wegener's granulomatosis vs.
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	Polyarteritis nodosa (PAN)
	*	
Respondent.	*	

Clifford J. Shoemaker and Renee J. Gentry, Vienna, VA, for petitioner.
James A. Reistrup, III, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

On February 13, 2004, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that a hepatitis B vaccination she received on March 6, 2001 caused her polyarteritis nodosa (hereinafter, "PAN"). On September 9, 2005,

[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.

petitioner filed an amendment to her petition, amending paragraph 5 to read that hepatitis B vaccinations in February 2001, on March 6, 2001, and on August 6, 2001 caused her PAN.

Respondent denied that petitioner had received more than one hepatitis B vaccine, accepting solely the vaccination administered on March 6, 2001. In addition, respondent denied that petitioner had PAN. Instead, respondent defended that petitioner has Wegener's granulomatosis (hereinafter,"Wegener's") and that the onset of her Wegener's was in 2000, the year before her hepatitis B vaccination, because she had mastoiditis in 2000 which can be the presenting sign of Wegener's.

The undersigned held a hearing on September 12, 2005. Testifying for petitioner were petitioner and Dr. Joseph A. Bellanti, an immunologist. Testifying for respondent was Dr. Alan I. Brenner, a rheumatologist.

FACTS

Petitioner was born on December 1, 1946.

On August 16, 2000, she saw Dr. Belinda E. Dickinson (this was a return visit but petitioner did not file the earlier record). Her right ear had been infected for three months. The infection was unresolved despite her taking Augmentin and drops through her family physician, who told her she had a right tympanic membrane perforation. On examination, Dr. Dickinson noted petitioner's right canal had diffuse erythema and mucoid drainage and debris, which she cleaned. The right drum was solid and the left ear clear. Dr. Dickinson diagnosed petitioner with CSOM (chronic serous otitis media) and otitis externa. She prescribed valsalva, Flonase for the nose, Augmentin, and alcohol to the right ear canal. Med. recs. at Ex. 5, p. 1.

On August 29, 2000, petitioner saw Dr. Dickinson. Her ears were no better. They were still draining and now she had pain in the mastoid area. Petitioner wanted a stronger antibiotic. *Id*

On September 5, 2000, petitioner returned to Dr. Dickinson with no improvement in her right ear blockage. While she was on Augmentin, her symptoms of mastoid tenderness worsened. Dr. Ruiz prescribed Cipro for her for ten days as well as a Medrol Dosepack. On examination, she had right ear inflammation with a solid drum and excessive middle ear fluid. The impression was CSOM of her right ear. She needed tube placement. Med. recs. at Ex. 5, p. 2.

On September 8, 2000, petitioner had a right unilateral tympanostomy with placement of a titanium bobbin. Med. recs. at Ex. 5, p. 3.

On September 13, 2000, petitioner was admitted to Holmes Regional Medical Center for Cleocin/Cipro IV antibiotic therapy because of chronic right ear infection, dizziness, and right eye discomfort. The history and physical of this operation was that petitioner had a right ear infection for four months. She had been on Augmentin as well as Cipro with Tobradex drops without relief. On September 8, 2000, she had a bobbin placed in her right tympanic membrane with debris sent for culture and sensitivity (which was returned as no growth). She was seen in Dr. Dickinson's office on September 13, 2000 with the tube in place, low volume tympanogram, and continued inflammation, infection, pain in her right ear and behind the right eye. Med. recs. at Ex. 5, p. 6.

A CT scan of the axial and coronal mastoids on September 13, 2000 showed extensive right mastoiditis (complete opacification of the right mastoid air cells) and extensive soft tissue

density in the right middle ear cavity and epitympanum (complete opacification of the middle ear cavity extending into the epitympanum and surrounding the ossicular chain). Med. recs. at Ex. 5, p. 7.

On September 14, 2000, Dr. Dickinson wrote a report stating chronic mastoiditis on the right with labyrinthitis and almost complete hearing loss. Med. recs. at Ex. 5, p. 10.

Also on September 14, 2000, Dr. Ronald D. Levy interpreted a bone scan of the right mastoid area. He concluded that there was a definite prominent area of increased uptake in the area of the right mastoid, findings that are most consistent with an inflammatory process in that area. Med. recs. at Ex. 5, p. 11.

On September 14, 2000, Dr. Dickinson examined petitioner in the hospital. Her right ear was actively draining. However, her ringing and dizziness were unchanged. She had chronic and acute right mastoiditis. Med. recs. at Ex. 5, p. 12.

On September 15, 2000, her dizziness decreased. She was otherwise unchanged. Dr. Dickinson discussed with petitioner and her husband her probable need for a right mastoidectomy if 72 hours of antibiotics did not resolve the situation. She had been on 36 hours of antibiotics. *Id.*

On September 16, 2000, petitioner had increased dizziness. She had a right mastoidectomy. *Id.* No fungus was isolated. Med. recs. at Ex. 5, p. 14.

On September 17, 2000, petitioner had morning dizziness on movement which improved through the day. She had mild postoperative ear pain and no change in her hearing. Med. recs. at Ex. 5, p. 18. She was discharged on September 19, 2000. *Id.*

On September 26, 2000, petitioner returned to Dr. Dickinson reporting that she was no longer dizzy and that her right ear pain was resolving. She had some anticipated numbness to her right external ear. She was on antibiotics. No active infection was identified. Med. recs. at Ex. 5, p. 19.

On October 11, 2000, petitioner returned to Dr. Dickinson. Her right ear was healed and the ear drum was solid. The bobbin was in place with thick mucous. *Id.*

On October 19, 2000, petitioner returned to Dr. Dickinson with increased pain in her right ear, right temple, right neck and occipital scalp. The examination showed the tube in place with no drainage. There was no inflammation or infection identified. Med. recs. at Ex. 5, p. 20.

On October 20, 2000, petitioner telephoned that she wanted a prescription for a sleeping pill (Ambian). *Id.*

On October 24, 2000, petitioner saw Dr. Miguel Mateos-Mora, an infectious disease specialist. She told him that she was having progressive worsening of pain behind her right ear in the mastoid area. The pain was so severe that she was taking two kinds of pain medications on a three- or four-hour basis without complete pain relief. She also felt pain in her ear. Med. recs. at Ex. 5, p. 21.

Also on October 24, 2000, petitioner had an MRI done of her brain/brainstem and cervical spine. There was definite fluid in the right mastoid air cells posteriorly and a fairly large pocket. There were a few scattered white matter lesions in the subcortical and deep white matter regions. This is occasionally seen in patients with migraine headaches. Med. recs. at Ex. 5, p. 22.

On October 25, 2000, petitioner returned to Dr. Dickinson with less right ear tenderness. Med. recs. at Ex. 5, p. 23.

On November 7, 2000, petitioner saw Dr. Dickinson. She was feeling much better. She had been off antibiotics for two weeks. Med. recs. at Ex. 5, p. 24.

On November 8, 2000, petitioner saw Dr. Dickinson. She had some ringing in her ears and intermittent pulsations. Med. recs. at Ex. 5, p. 25.

On November 30, 2000, petitioner saw Dr. Dickinson with mucoid drainage from her right ear. She had one day where her hearing improved suddenly and then was garbled and "reblocked." Dr. Dickinson's impression was acute otitis media. Med. recs. at Ex. 5, p. 26.

On December 4, 2000, petitioner had decreased inflammation and her tube was open. Dr. Dickinson recommended allergy testing. *Id.*

On December 19, 2000, petitioner saw Dr. Dickinson with intermittent episodes of improved hearing where her ear would suddenly "open up" and much improved unsteadiness. There was a large conduction loss on the right side. Dr. Dickinson's impression: "S L O W L Y resolving Mastoiditis right." Med. recs. at Ex. 5, p. 27.

On February 1, 2001, petitioner saw Dr. Dickinson who cleaned the right ear. There was a lot of mucous production. Petitioner was on allergy shots. Med. recs. at Ex. 5, p. 28.

On February 15, 2001, petitioner returned to Dr. Dickinson for an allergy shot and she wanted her right ear with tube checked. Dr. Dickinson suctioned thick mucoid discharge from the tube lumen. A bone scan was scheduled for that day. Med. recs. at Ex. 5, p. 29.

On February 15, 2001, a bone scan showed abnormal localization within the right mastoid region with minimal, slight improvement since the prior study of September 14, 2000, probably

related to the history of recent mastoidectomy. The area of localization might represent residual bone response to an underlying inflammatory, infectious process. Dr. Henry R. Zayas interpreted the bone scan. Med. recs. at Ex. 5, p. 30.

On February 20, 2001, petitioner saw Dr. Dickinson to discuss the results of the bone scan. She had chronic mucoid thin discharge from the tube in the right ear drum, which Dr. Dickinson cleaned. There was more mucous and debris in the mastoid and middle ear. Dr. Dickinson recommended that petitioner see other doctors or go to the Mayo Clinic because she felt with her training that she could not improve petitioner's status with another mastoidectomy. Med. recs. at Ex. 5, p. 31.

Petitioner received hepatitis B vaccine in February 2001 and on March 6, 2001according to a vaccination chart filled out at Quality Medical Care, Inc. Med. recs. at Ex. 1, p. 1. On May 23, 2001, she took a bone density test or DEXA of her spine and femur which were normal. She had complained of low back pain. Med. recs. at Ex. 3, p. 1. On August 6, 2001, petitioner received her third hepatitis B vaccination. Med. recs. at Ex. 1, p. 1. On September 17, 2001, petitioner had an x-ray done of her left ankle because of swelling and pain. Dr. Gerald Klein found no abnormality. Med. recs. at Ex. 3, p. 6. Also on September 17, 2001, Ms. Schrum was tested for antinuclear antibodies and was found to be negative. She was high however for rheumatoid factor. Med. recs. at Ex. 3, p. 7. On September 26, 2001, Dr. Manohar G. Reddy referred petitioner to Dr. David M. Spalding, a rheumatologist, with the diagnosis of polyarthralgia. Med. recs. at Ex. 3, p. 8.

On October 1, 2001, petitioner saw Dr. Spalding, complaining of multiple joint pain. She told Dr. Spalding that the onset of her bilateral knee and leg pain was two months earlier (which

would be August 2001). The pain was especially bad behind her knee. She had also started having wrist, elbow, and arm pain. She had a lot of local inflammation, and significant bilateral bicipital tendonitis and trochanteric bursitis causing arm and leg pain. Med. recs. at Ex. 2, p. 128.

On October 22, 2001, petitioner was diagnosed with Raynaud's syndrome, causing her fingers to go numb. Med. recs. at Ex. 2, p. 148.

She saw Dr. Spalding again on October 29, 2001, complaining of chest tightness and interference with breathing over the prior 24 hours. Med. recs. at Ex. 2, p. 118.

On November 9, 2001, petitioner had a kidney examination which showed small vessel disease. She was diagnosed with PAN because of tiny aneurysm formation. Med. recs. at Ex. 2, p. 264.

On November 11, 2001, petitioner had an MRI done on her brain which showed bifrontal deep white matter foci of altered signal, which was nonspecific. Med. recs. at Ex. 2, p. 280.

On November 15, 2001, on discharge from Holmes Regional Medical Center, petitioner was diagnosed with PAN. Dr. Spalding wrote that Ms. Schrum had a past history of an atypical granulomatous infectious process and was treated by an ENT about a year previously and it finally stabilized. Her ANCA (antineutrophil cytoplasmic antibody) was positive for c-ANCA (cytoplasmic pattern corresponding to ANCA with specificity for proteinase-3). She had severe vasculitis with severe ischemic involvement of her hands. Med. recs. at Ex. 3, p. 15.

On November 20, 2001, Dr. Spalding diagnosed petitioner with PAN with a remote possibility that she actually had Wegener's in view of her positive c-ANCA, but her arteriograph

showed aneurysm which would make it almost certainly PAN rather than Wegener's. She did not appear to have ongoing inflammatory disease. Med. recs. at Ex. 3, p. 17.

On November 20, 2001, Dr. Dickinson wrote a note in the records to Dr. Anderson that petitioner had developed a sudden onset of PAN with compromise of the blood supply to her finger tips. She had some surgery to revascularize her digits and was on chronic steroid therapy. Her rheumatologist, Dr. Spalding, notified her that if her sedimentation rate did not go down, he might have to add Cytoxan to her medications. Dr. Dickinson had not given petitioner an allergy shot since October 25, 1001 and was holding off until her autoimmune disease was better controlled. Med. recs. at Ex. 5, p. 33.

A Medical Release dated November 19, 2003 from MIMA for Drs. Gilbert and Spalding states, among many medical problems, that petitioner has PAN and Wegener's Granulomatosis. Med. recs. at Ex. 2, p. 3.

Petitioner saw Dr. Spalding on February 5, 2004 for residual nasal stuffiness, right leg tightness and ache, and interference with sleep. Dr. Spalding discussed the significance of petitioner's having had hepatitis B vaccination within six months of her onset of this disease with no prior symptoms before the hepatitis B and indicated that there is a known form of polyarteritis nodosa that occurs after natural hepatitis B infection. He speculated on the possibility of the vaccination's having triggered the response but there was no way to prove it. It remained a speculation. Med. recs. at Ex. 4, p. 1.

Other Submitted Material

Petitioner filed three statements from various people, none of which is sworn. Petitioner filed a statement from Ada Y. Webb, a friend of petitioner for 30 years. P. Ex. 6. Ms. Webb

states that shortly after petitioner's February 2001 hepatitis B vaccination, her health began to deteriorate and she went to Dr. Spalding. *Id.*

Petitioner filed a statement from Carolyn K. Smith, another friend. P. Ex. 7. She states that, almost immediately after petitioner received her hepatitis B vaccination in February 2001, petitioner's arms began to ache and her energy declined. She also states that, after petitioner's second hepatitis B vaccination in March 2001, petitioner had deep pain in her hips, aches in her joints, and a decline in energy and mobility. She lastly states that, after petitioner's third hepatitis B vaccination in August 2001, petitioner's decline was remarkable: constant pain, significant loss of energy and mobility, and loss of quality of life. *Id.*

Petitioner filed the statement of L. Mecove Schrum, who met petitioner in July 1991. P. Ex. 8. It is unclear what relationship Mr. Schrum has to petitioner, but he seems to be her husband. He recounts how her energy level has dropped profoundly. *Id.*

Among articles from the medical literature that petitioner filed as Ex. 10 is a case report entitled "Suspected Hepatitis B Vaccination Related Vasculitis," by C. Le Hello, et al., 26 *J Rheumatol* 191-94 (1999). P. Ex. 10, p. 13. The authors describe three cases of vasculitis developing after the vaccinees received recombinant hepatitis B vaccine. In the first case, a 16-year-old girl developed transient palpable purpura on her arms 20 days after receiving recombinant hepatitis B vaccine. Fifteen days later, she had new purpuric lesions on her legs, associated with abdominal pain, arthralgias, and myalgias. *Id.* In the second case, a 16-year-old girl developed palpable purpuric lesions seven days after receiving recombinant hepatitis B vaccine. She had arthralgias of the knee, finger, toe, and elbow. *Id.* In the third case, a 19-year-

old woman developed arthralgias, left-side hemihypesthesia, and unstable gait seven days after receiving the third recombinant hepatitis B vaccine. *Id.*

In Table I, the authors list seven other articles discussing cases of vasculitis following recombinant hepatitis B vaccination. *Id.* at 14. They state, with reference to the three cases they report, that the chronology of events and the exclusion of other identifiable etiologies or historical factors suggested vaccine-induced vasculitis. *Id.* They state: "Vaccine-induced vasculitides have also been reported with some other antiviral vaccines." *Id.* at 15. Although the exact biological mechanism is hypothetical, it is probably immune-mediated. *Id.* They note that such reactions have also been described in hepatitis B virus infection. *Id.* They call attention to the danger of exposing a patient with acute vasculitis, especially systemic disease, to rechallenge with the vaccine. *Id.*

Another article in petitioner's Ex. 10 is entitled "Rheumatic disorders developed after hepatitis B vaccination," by J.F. Maillefert, et al., 38 *Rheumatology* 978-83 (1999). P. Ex. 10, p. 17. The authors discuss 22 patients of which three (all women) had vasculitis with onsets at one week, two weeks, and two months after vaccination. *Id.* at 19. The authors pose several pathogenetic models to explain rheumatic disorders following hepatitis B vaccination. *Id.* at 20. Some of these are deposition within the synovium of circulating immune complexes containing viral antigen and anti-hepatitis B surface antibodies, or triggering the illness in individuals with underlying genetic and immunological susceptibility. *Id.* at 20-21. The authors noted that the manifestations worsened in most patients who received a further vaccination. *Id.* at 21.

Another article in petitioner's Ex. 10 is a short communication entitled "Major adverse reactions to yeast-derived hepatitis B vaccines–a review," by I. Grotto, et al., 16 *Vaccine* 4:329-

34 (1998). P. Ex. 10, p. 23. The authors state that immune complexes containing hepatitis B surface antigen have been detected in the sera and tissues of patients with acute and chronic hepatitis B infection, and in asymptomatic carriers. *Id.* at 27. Immune complex diseases including PAN have been associated with the prodromal phase of acute hepatitis B possibly through the mechanism of activation of the complement system by immune complexes. *Id.* at 27. They continue that hepatitis B vaccine administration may lead to a large amount of antigen and small amounts of antibodies in the serum similar to the prodromal phase of hepatitis B infection, which induces the formation of soluble antigen-antibody complexes, initiating clinical disease. *Id.*

Another article in petitioner's Ex. 10 is entitled "Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption," by F. De Keyser, et al., 18 *Clin & Experimental Rheumatology* 81-85 (2000). P. Ex. 10, p. 31. The authors state that the association of hepatitis B infection with vasculitis of the small- or medium-sized blood vessels illustrates the broad spectrum of immune-mediated clinical manifestations associated with hepatitis B infection. *Id.* They report two cases of arteritis of medium-sized vessels and one case of major skin eruption after administration of hepatitis B vaccine. In the first case, a 41-year-old policeman received two doses of hepatitis B vaccine. Two weeks after the first vaccination, he had myalgia, joint pain, and morning stiffness. One month after the first vaccination, he had the second one. After that, the patient's arthralgias and myalgia increased and he developed an ulcer over the left lower limb and lesions on his hands. He had positive ANCA fluorescence (confirmed by positive anti-proteinase-3 ELISA). Skin biopsy of the left lower limb ulcer revealed granulation tissue. He was diagnosed with PAN. *Id.*

The second case concerned a 35-year-old nurse who received a second dose of hepatitis B vaccine five years after her first dose. Two weeks after the second dose, she had a fever with myalgia and coughing which went away but recurred two weeks later. She had a third relapse of symptoms after a two-week interval. She also had a skin rash over the lower limbs and elevation of fever. Her anti-hepatitis B surface antibodies were strongly positive. She was diagnosed with PAN. *Id.* at 32.

The authors comment that, in the first case, the occurrence of anti-proteinase 3 after vaccination was highly unusual. Anti-proteinase 3 antibodies or c-ANCA can be found in 10% of patients diagnosed with PAN. In the second case, the small blood vessels were spared. The second case, but not the first, had clearly positive hepatitis B serology. In reflecting on the established relationship between hepatitis B infection and PAN, the authors muse:

> In view of the fact that the complete hepatitis B virus may induce an immune pathology, including vasculitis, induction of such complications by immunization with specific hepatitis B-related antigens should not be totally unexpected. However, case reports on such associations are rare.

Id. at 33-34. The authors then discuss other case reports.

Returning to the first two cases in this article, the authors propose a biological mechanism for hepatitis B vaccine causing PAN:

> One may postulate that the HBs [hepatitis B surface] antigen behaves like a classical heterologous protein and induces the formation of immune complexes. As in acute serum sickness, these immune complexes may then mediate the pathology.

Id. at 34.

Petitioner filed her rheumatologist Dr. David Spalding's note of April 18, 2005, stating, "The attached clearly supports my original opinion that Mrs. Schrum had Polyarteritis Nordosum [sic] rather than Wegener's Granulomatosis. I consider the aneurysm findings on the arteriograms more important than the positive C-ANCA." P. Ex. 12, p. 1. Attached is an angiogram, dated November 9, 2001, which Dr. Thomas R. Foster interprets as showing small vessel disease. "Findings in the kidney do suggest polyarteritis nodosum in terms of irregularity stenosis and tiny aneurysm formation." *Id.* at 6. Also attached is Dr. Spalding's medical record dated November 20, 2001, in which he states that petitioner has polyarteritis nodosa with a remote possibility that she actually has Wegener's granulomatosis in view of her positive c-ANCA, but her arteriography showed aneurysm and "that would make it almost certainly polyarteritis rather than Wegener's." *Id.* at 7.

Petitioner filed an article entitled, "Polyarteritis Nodosa Reports to the Vaccine Adverse Event Reporting System (VAERS): Implications for Assessment of Suspected Vaccine-Provoked Vasculitis," by E.M. Begier, et al., 31 *J Rheumatol* 2181-88 (2004). P. Ex. 14. They describe PAN as "a rare life-threatening form of necrotizing vasculitis affecting medium-size arteries, with a well documented association with hepatitis B virus (HBV) infection. Multiple case reports have suggested a link between PAN and hepatitis B vaccination [footnotes omitted]." P. Ex. 14, p. 1. The undersigned notes that Dr. Spalding recorded that petitioner has small vessel disease in her kidneys. Med. recs. at Ex. 2, p. 264. The authors of P. Ex. 14 cite a definition of the Chapel Hill Consensus Conference [CHCC] defining PAN as "'necrotizing inflammation of medium-size or small arteries *without* glomerulonephritis or vasculitis in arterioles, capillaries or venules.'" P. Ex. 14, p. 2. The authors classified reports as "definite" PAN cases if they

described a tissue biopsy with medium-size vessel vasculitis or an angiogram documenting microaneurysms. *Id.* Petitioner herein had tiny aneurysm formation in her kidneys shown by arteriograph. Med. recs. at Ex. 2, p. 264.

The authors continue, "Current hepatitis B vaccines contain hepatitis B surface antigen (HBsAG) produced in yeast cells using recombinant DNA techniques.... [footnote omitted]." P. Ex. 14, p. 1. "VAERS is a passive surveillance system jointly administered by the US Food and Drug Administration and Centers for Disease Control for post-licensure vaccine safety surveillance...." *Id.* at 2. From 1990 through 2001, 25 cases of PAN were reported to VAERS. Two were reclassified as microscopic polyangiitis because of the presence of glomerulonephritis. Among the 23 remaining PAN reports, they classified 9 as definite PAN, 6 possible, and 8 indeterminate. *Id.* Ten cases has no other documented etiology for PAN than the vaccine. *Id.* The modal peak of onset was two weeks post-vaccination. *Id.* There were three cases of rechallenge. *Id.* at 4.

In discussing biological plausibility, the authors state:

> HBV-associated PAN is generally considered to be part of the subset of systemic vasculitides whose pathogenesis involves immune complex deposition in vessel walls. Hepatitis B surface antigen has long been held to be the antigen responsible for the pathogenic immune complex formation in HBV-associated PAN. Hepatitis B surface antigenemia has been documented to frequently follow hepatitis B vaccine and has been detected up to 18 days after the 20 μg vaccine, increasing the biological plausibility of related immune complex-mediated disease.
> However, several lines of evidence have challenged the role of hepatitis B surface antigen-antibody immune complexes in mediating PAN, suggesting that hepatitis B proteins other than surface antigen may be involved. First, hepatitis B surface antigen-antibody immune complexes can be found in infected patients who do not have vasculitis. Second, disease activity and clearance of

> symptoms have been better correlated with HBV replication as measured by HBV DNA levels and hepatitis E antigen/antibody seroconversion than with HBV surface antigen levels. Finally, recurrence of PAN is rare in patients who have undergone hepatitis E antigen/antibody seroconversion despite continued hepatitis B surface antigenemia [footnotes omitted].

Id. at 4-5.

The authors discuss analogy with reference to other similar illnesses following hepatitis B vaccination:

> Other immune complex-mediated illnesses have been anecdotally associated with the hepatitis B vaccine. A "serum-sickness-like" hypersensitivity syndrome of delayed onset occurring days to weeks after vaccination has been reported to follow the 20 µg vaccine in passive post-marketing surveillance. Case reports and case series of other immune complex diseases including glomerulonephritis have been published [footnotes omitted].

Id. at 5.

The authors found partial support for a plausible temporal association, biologic plausibility, analogy, and dose responsiveness (most cases occurred after two doses), but considered documentation inconclusive to rule out other infections and noted reporting bias, especially from France. Moreover, the pathology needed to be worked out more definitively. *Id.* at 6.

Petitioner filed an excerpt from Cecil Textbook of Medicine, 20th Ed. (1996). P. Ex. 15. In a section describing the vasculitic syndromes, L.J. Rosenwasser states:

> Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of the blood vessel wall. ....
> The vasculitic syndromes are generally thought to result from immunopathogenic mechanisms....Among these mechanisms, the deposition of circulating immune complexes with subsequent

> vessel damage has emerged as a major immunopathologic event associated with most of the vasculitic syndromes....

Id. at 3.

Dr. Rosenwasser comments, "The heterogeneity and the obvious overlap among the vasculitic syndromes have led to difficulties in classification of this group of diseases." *Id.* at 4. PAN "manifests features such as small and medium-sized muscular artery involvement...." *Id.*

In a section describing PAN, Dr. Rosenwasser states, "The association of hepatitis B antigen-antibody complexes and polyarteritis provides strong support for the hypothesis that the vasculitides in general are secondary to the deposition of soluble immune complexes." *Id.* at 5.

In a section describing Wegener's Granulomatosis, N.B. Allen states that "necrotizing granulomatous vasculitis is the hallmark disorder in the lower respiratory tract." *Id.* at 8. Wegener's is associated with the cytoplasmic pattern of anti-neutrophil cytoplasmic antibody (c-ANCA) and more specifically with antibodies against proteinase 3 (PR-3), a serine protease found in neutrophils. *Id.* The spectrum of clinical presentations and organ system involvement in Wegener's is broad, involving predominantly the upper and lower respiratory tracts and the kidneys, with classic presentations involving sinusitis, serous otitis media, rhinitis with nasal ulcerations, cough, hemoptysis, and constitutional symptoms. *Id.* Patients usually seek help due to upper and/or lower respiratory complaints, including ear pain. Some experience months or years of these symptoms before diagnosis. *Id.*

Petitioner filed excerpts from Harrison's Principles of Internal Medicine, 13th Ed. (1994). P. Ex. 16. In a chapter on the vasculitic syndromes, A.S. Fauci states that there is considerable overlap among the vasculitic syndromes. *Id.* at 4. Dr. Fauci states that "many reports of PAN

actually have included diseases other than the classic syndrome." *Id.* Sufficient to make the diagnosis are aneurysms of small- and medium-sized arteries in the renal, hepatic, and visceral vasculature on angiogram. *Id.* at 5. Wegener's involves disseminated vasculitis in small arteries and veins. *Id.* at 7.

On November 3, 2005, Dr. Spalding wrote a letter in response to the undersigned's Order questioning whether petitioner had PAN or Wegener's or both. P. Ex. 18. Dr. Spalding states he has never encountered a case of overlap of Wegener's and PAN, and it would be a rare occurrence. He felt that the pathologic identification of aneurysms on petitioner's arteriogram was the overwhelmingly important diagnostic factor for his stating petitioner has PAN. He had never or subsequently seen aneurysm formation in a patient with Wegener's. He has seen patients with other connective tissue diseases who had positive c-ANCAs without having Wegener's. Therefore, he felt and still feels that petitioner's case is best explained by PAN. There was no pathologic documentation of vasculitis or granulomatous disease in any of petitioner's otolaryngologists' records. He thinks petitioner's mastoiditis was an unrelated pathologic condition and not the first manifestation of Wegener's. Dr. Spalding does not know the cause of petitioner's PAN. *Id.*

Petitioner filed a letter dated October 31, 2005 from petitioner's otolaryngologist Dr. Belinda Dickinson. P. Ex. 19. Dr. Dickinson attaches a pathology report from Dr. Silverstein who performed another mastoidectomy on petitioner April 17, 2001. She states it did not show granulation tissue and only chronic inflammation, which one would expect with chronic ear infection. She also attaches her own pathology report from the first mastoidectomy, dated September 16, 2000, and a letter. *Id.* at 1.

Dr. Dickinson states that petitioner had been her patient since January 30, 1992. After a prolonged absence, petitioner returned to Dr. Dickinson on August 16, 2000 with a right ear infection of two to three months' duration. She had a titanium bobbin placed on September 8, 2000 to remove middle ear fluid for culture. Using Cipro and Tobradex did not resolve her ear infection and petitioner rapidly progressed to a right mastoid infection requiring admission on September 13, 2000 with intravenous Cleocin, Cipro, and Decadron. This did not heal the ear infection and on September 16, 2000, petitioner had a right mastoidectomy. The pathology report of the tissue removed confirmed chronic inflammation and granulation tissue, but did not indicate Wegener's. Petitioner then had a second mastoidectomy with Dr. Silverstein in April 2001, and his pathology report confirmed no evidence of Wegener's. Dr. Dickinson states that Wegener's has three distinct pathologic findings: necrotizing granulomatous lesions in the upper respiratory tract (which petitioner did not have); glomerulitis with necrosis and thrombosis of the renal arterial system (which petitioner did not have); and generalized focal necrotizing vasculitis involving arteries and veins (which petitioner had but no longer has). Wegener's is a progressive and unrelenting disease, and Dr. Dickinson does not believe she had it. *Id.* at 2.

Page 3 of Ex. 19 is Dr. Herbert Silverstein's pathology report. Dr. James E. Eadens states there was moderate chronic inflammation, but no granulomas in the right mastoid area. Pages 4-5 of Ex. 19 is Dr. Dickinson's pathology report. Dr. Robert Huberman states that there was chronic inflammation and granulation tissue in the right mastoid. Immunohistochemical studies revealed a mixed B and T cell population compatible with a reactive process.

Petitioner filed Dr. Bellanti's report, dated November 28, 2005. P. Ex. 20. Dr. Bellanti states he agrees with Dr. Spalding that an overlap of Wegener's and PAN is extremely rare and

not appropriate in this case. The aneurysm findings, together with Dr. Dickinson's pathology reports, are significant with respect to a diagnosis. Dr. Spalding is a highly-regarded rheumatologist with 25 years' experience. Petitioner had a chronic ear inflammation with infection rather than the granulation tissue that is the distinctive marker of Wegener's. *Id.*

Respondent filed Dr. Brenner's report, dated February 12, 2006. R. Ex. AA. He states that evidence of kidney inflammation rules out the diagnosis of PAN. *Id.* at 2. He also states that PAN is not an ANCA-associated condition. *Id.* The incidence of PAN has declined dramatically since the introduction of hepatitis B vaccine. He rejects the diagnosis of PAN in petitioner's case because she has an ANCA-associated small vessel vasculitis with the specific c-ANCA representing anti-proteinase 3, almost always a pathologic marker of Wegener's which he believes she had, and Wegener's manifested before she received hepatitis B vaccine. *Id.* at 2-3. .

Petitioner filed Dr. Bellanti's letter, dated March 17, 2006. P. Ex. 21. Dr. Bellanti states that the medical theories of causation linking PAN to hepatitis B vaccination would also apply to Wegener's. He believes that PAN and Wegener's can overlap. The statement that PAN is never associated with ANCA is untrue. Hepatitis B vaccine can cause nephritic syndrome. Dr. Bellanti agrees with Dr. Spalding that the presence of aneurysms in petitioner overwhelmingly points to PAN. *Id.* He doubts Dr. Brenner's assertion that the vaccine cannot cause PAN because there is no replicating viral antigen as there is for natural hepatitis B infection. Dr. Bellanti states there is sufficient surface antigen in hepatitis B vaccine to convey immunity and also provide sufficient surface antigenemia to cause immunologically-mediated immune complex reactions, such as PAN. He notes that the Begier article (P. Ex. 14, R. Ex. BB) supports his opinion because it contains three cases of rechallenge, and hepatitis B surface antigenemia has been documented to

follow hepatitis B vaccination up to 18 days after vaccination, increasing the biologic plausibility of the vaccination causing immune-complex mediated disease. *Id.* at 2.

Dr. Bellanti also agreed with Dr. Dickinson's analysis of three distinct pathologic findings of Wegener's, the first two of which petitioner does not have, and the third which she had but no longer has. He agreed with Dr. Dickinson that Wegener's is usually progressive and unrelenting, which does not describe petitioner's condition. He agreed with Dr. Dickinson that the pathology reports are not diagnostic of Wegener's. *Id.*

Respondent filed an article entitled "Rheumatic Disorders Developed after Hepatitis B Vaccination," by J.F. Maillert, et al., 38 *Rheumatology* 978-83 (1999). R. Ex. C. The authors surmise "that hepatitis B immunization might trigger the onset or the relapse of the diseases in individuals with underlying genetic and immunological susceptibility [footnote omitted].} *Id.* at 981-82. There were several arguments in favor of a causal relationship, but the epidemiology was not supportive. *Id.* at 982.

Respondent filed a case report entitled "Large Artery Vasculitis Following Recombinant Hepatitis B Vaccination: 2 Cases," by A. Zaas, et al., 28 *J Rheumatol* 1116-20 (2001). R. Ex. F. The authors note that in all but one of the prior reports of vasculitis associated with hepatitis B vaccination, the individuals had small- or medium-sized vessels affected. The one vaccinee with larger artery disease had had plasma-derived vaccine. The authors discuss two cases of women who received recombinant hepatitis B vaccine and had large artery vasculitis. The authors state, "Small vessel vasculitides ... that develop after infection or vaccination have been attributed to an immune complex mediated process." *Id.* at 1119. They surmise their cases may have developed through a similar process.

Respondent filed a case report entitled "Ruptured arterial aneurysm of the kidney in a patient with Wegener's granulomatosis," by R. Senf, et al., 18 *Nephrol Dial Transplant* 2671-73 (2003). R. Ex. O. The authors discuss a 35-year-old man who had Wegener's (pulmonary manifestation and positive PR3-ANCAs with necrotizing granulomatous inflammation) but also a large left-sided perinephric hematoma. Angiography showed multiple impressive aneurysms in splanchnic, hepatic, and renal arteries. *Id.* at 2671. The authors conclude that a clear-cut differentiation of particular vasculitides according to the Chapel Hill Consensus Conference may be impossible because of significant overlap of clinical presentations. *Id.* at 2672.

Respondent filed an article entitled "Large vessel aneurysms in Wegener's granulomatosis," by D. Shitrit, et al., 36 *J Vasc Surg* 856-58 (2002). R. Ex. P. The authors define Wegener's as affecting small- and medium-sized granulomatous vasculitis of the upper and lower respiratory tracts and renal involvement. *Id.* at 856. The patient they describe had an unusual case of Wegener's with large-vessel aneurysm.

Respondent filed an article entitled "Rupture of a Hepatic Artery Aneurysm Caused by Wegener's Granulomatosis," by M.A. den Bakker, et al., 193 *Pathol Res Pract* 61-66 (1997). R. Ex. Q. The authors state that Wegener's involves small- and medium-sized blood vessels and manifests itself particularly in the respiratory tract and kidneys. *Id.* at 61. Histological similarity to PAN is also seen, although PAN does not involve arterioles and does not result in cavitary pulmonary lesions. *Id.* Features in this case demonstrate considerable overlap with other forms of vasculitis. "Segmental involvement with or without fibrinoid necrosis and aneurysm formation is more typical of polyarteritis nodosa, and aneurysms of the hepatic artery have been described in polyarteritis nodosa." *Id.* at 65. The authors note that positive c-ANCAs are seen

only in about 10% of patients with PAN. *Id.* "The case presented here clearly presents features suggestive of both [Wegener's] and polyarteritis nodosa, suggesting a vasculitis overlap syndrome." *Id.*

Respondent filed a guest editorial entitled "Otological Wegener's Granulomatosis at the Time of Initial Presentation: a Potential Diagnostic Dilemma," by A. Ferlito, et al., 123 *Acta Otolaryngol* 675-77 (2003). R. Ex. R. The authors state that Wegener's was first described in 1931 as an atypical form of PAN. *Id.* at 675. Some patients may develop a localized form of Wegener's which is limited to the upper and/or lower respiratory tracts. *Id.* Otologic manifestations of Wegener's may range from ear pain to aural discharge to aural polyp formation to loss of hearing. Otological involvement varies from 19% to 61% of patients. *Id.* Unilateral or bilateral serous otitis media is the most common otological manifestation of Wegener's. *Id.* at 123. Chronic otitis media usually is related to middle ear and mastoid cavity involvement in Wegener's. *Id.*

Respondent filed an article entitled, "Clinical Review of Wegener's Granulomatosis," by H. Nagai, et al., *Acta Otolatyngol* Supp. 547:505-3 (2002). R. Ex. S. The authors state that the most common primary complaints of patients with Wegener's were nasal symptoms, including nasal bleeding, obstruction, and discharge. Vertigo and hearing loss were seen in a smaller number of patients. *Id.* at 50. An infection may precede the development of Wegener's. *Id.* Pathological manifestations were mucosal ulceration, acute and chronic inflammation, vasculitis, necrosis, and granulomatosis. *Id.* at 51.

Respondent filed an article entitled "Wegener's Granulomatosis Presenting with Otologic Manifestations," by A. Rinaldo, et al., 28 *J Otolaryngology* 6:347-50 (1999). R. Ex. T. The

authors state that Wegener's is characterized by an inflammatory reaction pattern (necrosis, granulomatous inflammation, and vasculitis) occurring in the upper and lower respiratory tracts and kidneys. *Id.* at 347. They discuss two cases. The first involved a woman with a six-month history of left otalgia, hearing loss, nasal obstruction, and frontal headache. She was diagnosed with otitis media with effusion. She had multiple pulmonary nodules which, on biopsy, showed nonspecific chronic inflammation. Multiple biopsies of the nasal mucosa showed erosive inflammatory tissue with granulocytic and lymphocytic cells, necrotizing vasculitis with thrombocytosis, and multinucleated giant cells. *Id.* The second case involved a woman with a three-month history of bilateral otalgia and hearing loss, right otorrhea, and nasal obstruction. *Id.*

The authors discuss a limited form of Wegener's which does not include renal involvement. *Id.* at 348. The nasal cavity and paranasal sinuses are the most common sites of involvement in the head and neck area, whereas otologic disease is found in fewer cases. Otologic involvement may occasionally be the first and unique sign of Wegener's. Mastoiditis may be the first manifestation of Wegener's. *Id.*

Respondent filed an article entitled "Wegener's Granulomatosis Presenting as Mastoiditis," by A. E-M Moussa and K.A. Abou-Elhmd, 107 *Ann Otol Rhinol Laryngol* 560-63 (1998). R. Ex. U. The authors state that Wegener's is an autoimmune disease. *Id.* at 560. The authors report two cases in which the first symptom of Wegener's was mastoiditis. The first involved a girl with a history of right otalgia, fever, and sudden hearing loss. Ear tubes and antibiotics did not resolve the situation. Her nasal cavities were normal. *Id.* Renal biopsy showed patchy necrosis and the patient died. *Id.* at 561. The second case involved a woman with a history of fever, left earache and discharge, dizziness, tinnitus, and nasal blockage. *Id.*

Histopathology showed granulation tissues and inflamed connective tissue. *Id.* at 562. The authors note that otological manifestations in Wegener's are almost always secondary to nasal involvement. *Id.* For aural symptoms to be the only presenting problem is rare. *Id.* The authors suggest that if someone presents with a mastoiditis unresponsive to conventional medical and surgical therapy after more than one month, the diagnosis of Wegener's should be considered. *Id.*

TESTIMONY

Ms. Schrum testified first for petitioner. At the end of October 2000, she had an ear infection. Tr. at 5-6. [The undersigned notes that Ms. Schrum saw Dr. Dickinson on a return visit on August 16, 2000, complaining of an ear infection that had lasted three months. That puts the onset of petitioner's ear infection as May 2000. We know from the medical records that petitioner's first mastoidectomy was done on September 16, 2000. Dr. Robert Huberman noted fibrous tissue with chronic inflammation and granulation tissue. Petitioner's second mastoidectomy was done on April 17, 2001. Dr. James E. Eadens noted moderate chronic inflammation but no granulomas. Ms. Schrum's right ear problem lasted at least 11 months. Dr. Dickinson did the first mastoidectomy. Dr. Silverstein did the second.] Ms. Schrum had been prescribed various antibiotics which did not help her ear infection. Tr. at 6-8. Even tubes did not help. Tr. at 8.

Ms. Schrum retired in March 2000 and began working as a part-time courier for a medical group at the end of 2001. Tr. at 10-12. Her employer required her to receive hepatitis B vaccinations. Tr. at 14. After the first vaccination, her fingers started to ache two to three weeks later. Tr. at 18-19. After the second hepatitis B vaccination on March 6, 2001, her hands ached

more and then her shoulders, knees, and legs ached from one to two weeks after vaccination. TR. at 21-22. She did not have any fever. Tr. at 22.

Ms. Schrum states she had a bone scan on May 23, 2001. Tr at 22-23. [This was not a bone scan. This was a bone density test or DEXA. Ms. Schrum's complaint was low back pain. The results of her test showed her spine and femur to have normal density. Med. recs. at Ex. 3, p. 1.]

Ms. Schrum found it harder to walk and saw Dr. Manohar G. Reddy, an internist, who put her on Vioxx. Tr. at 23. By June and July 2001, she was getting worse and Dr. Reddy doubled the Vioxx. Tr. at 25.

On August 6, 2001, Ms. Schrum received her third hepatitis B vaccination. Tr. at 26. One week later, her pain increased in her feet and arms, and she could not get out of a chair. Tr at 27. On September 26, 2001, Dr. Reddy referred her to Dr. Spalding to rule out systemic lupus erythematosis or rheumatoid arthritis. Tr. at 28. She saw Dr. Spalding between October 1 and 3, 2001, and he thought she had bursitis. Tr. at 29-30. She was still working. Tr. at 31. On October 17, 2001, she saw Dr. Spalding and reported decreasing and increasing pain. Tr. at 32. Following this visit with Dr. Spalding, Ms. Schrum went to Dr. Dickinson's office to receive an allergy shot. Tr. at 33. During the visit, Dr. Dickinson observed some discoloration on Ms. Schrum's fingers, which she suspected might be Raynaud's disease, and advised her to see Dr. Spalding. Tr. at 34.

Ms. Schrum testified that on October 22, 2001, she visited Dr. Spalding's office and asked his nurse to inform him of Dr. Dickinson's suspicions regarding Raynaud's disease. Tr. at 34. Ms. Schrum called Dr. Spalding's office on October 24, 2001 to complain of numbness in

her fingers. Tr. at 35. By October 29, 2001, Ms. Schrum could hardly walk. Tr. at 38. She was hospitalized for an initial two and one-half week period on November 2, 2001 at Holmes Regional Medical Center in severe pain. Tr. at 38, 41. On the first day of her hospitalization, she thought she was dying. Tr. at 39. She received morphine for the pain, and Dr. Spalding diagnosed her with PAN. She received chemotherapy and Prednisone. Tr. at 41. She lost her hair and gained weight. Tr. at 45-46. She was on chemotherapy for two and one-half years. Tr. at 47.

Dr. Peter Gilbert, a nephrologist, asked to consult in the hospital, indicated in his notes following a December 21, 2001 office visit, that Ms. Schrum had an arteriogram showing microaneurysms in her kidney. Tr. at 51. Dr. Spalding opined that the aneurysms were indicative of PAN and not Wegener's granulomatosis. Tr. at 52. Ms. Schrum further testified that Dr. Spalding's opinion was not disputed by any other doctors she consulted. *Id.*

Following her initial hospitalization, Ms. Schrum began chemotherapy treatments for PAN. Tr. at 53. She saw Dr. Spalding once a week. *Id.* As a result of the treatments, her white blood count decreased and she was hospitalized for a four-day period in March or April 2002 for treatment of flu-like symptoms. Tr. at 55. Even though her PAN has gone into remission, her legs and shoulders still hurt. Tr. at 56. She still has a low white blood cell count and low energy. *Id.* She takes Prednisone daily. Tr. at 62-63.

Dr. Joseph Bellanti, an immunologist, testified next for petitioner. Tr. at 85. His opinion is that petitioner has PAN but not Wegener's. Tr. at 90-91. He stated that Wegener's is a "distinct clinical pathological entity" involving the upper and lower respiratory tracts plus the kidneys and lungs. Tr. at 92-93. Ms. Schrum did not have involvement of her lungs. Tr. at 95-

96. She did not have involvement of her nose or sinuses. *Id.* While c-ANCA is normally associated with Wegener's, in 10% of PAN cases, the c-ANCA is positive. Tr. at 96-98. Dr. Bellanti described a condition known as "overlap syndrome" where a person has PAN but exhibits symptoms of other vasculitides, including Wegener's. Tr. at 100. He stated that in the present case, there is not enough to diagnose an overlay between PAN and Wegener's, and opined that Ms. Schrum has classic PAN despite the presence of c-ANCA. *Id.*.

Dr. Bellanti's opinion is that hepatitis B vaccine caused petitioner's PAN because natural hepatitis B infection is linked to PAN. Tr. at 101. Upon questioning by the undersigned, Dr. Bellanti further stated that he believes that Ms. Schrum's aches after her first hepatitis B vaccination could be the onset of her PAN. Tr. at 102. Her second hepatitis B vaccine gives more support to diagnosing PAN because she had pain exacerbation within two weeks. Tr. at 103. After her third hepatitis B vaccination, she had symptoms within one week. *Id.* Dr. Bellanti referred to this process as a classic anamnestic or booster response or positive rechallenge. Tr. at 103-04.

Dr. Bellanti stated it is biologically plausible that hepatitis B vaccine causes PAN. Tr. at 104. He then described how PAN is caused and the involvement of the body's immune complexes. Tr. at 105. Around or partly around the blood vessel, there is necrosis due to a Type III immune complex injury where the antigen and antibody come together, with fixed complement, resulting in an influx of cells, which causes inflammation. *Id.* Upon dying, these cells release proteolytic enzymes which destroy the vessel, weakening the vessel wall and causing the "outpocketing" known as microaneurysm. *Id.*

In cases of PAN reported to VAERS, there was a peak of onset at two weeks post-hepatitis B vaccination. Tr. at 110-11. Dr. Bellanti testified that the association between hepatitis B vaccine and PAN is further supported by documented accounts of hepatitis B surface antigenemia (i.e., the presence of antigens in the blood) for up to 18 days following vaccination. Tr. at 115. Antigenemia, or the presence of antigens in the blood, indicates that there is a viral agent in the blood. Tr. at 116. Dr. Bellanti stated that, in his opinion, there is no alternate etiology for Ms. Schrum's PAN. Tr. at 134-35.

On cross-examination, Dr. Bellanti distinguished classic from non-classic PAN, stating that classic PAN does not involve the pulmonary system, and can be described as a "multi-system necrotizing vasculitis of the small and medium-sized muscular arteries in which the involvement of the renal and visceral arteries is characteristic." Tr. at 136. The difference between hepatitis B infection and hepatitis B vaccine is that the latter does not have replicating antigen. Tr. at 150. When the antigen gets into the blood, you get antigen-antibody-complement circulating in the blood. Tr. at 151. Type III immune complex deposition involves inflammation, weakening of the cell wall, and aneurysm. Tr. at 150. Hepatitis B vaccine is less virulent than the viral infection. When you have antigenemia, the ingredients are there for an immune complex injury. Tr. at 152-53. PAN is an expression of immune complex disease. Tr. at 153. All vasculitides have inflammation and damage to blood vessels mediated by immunopathogenetic mechanisms. Tr. at 161. Granulomas are tissue responses to infection. Tr. at 169. Wegener's affects the smaller blood vessels, whereas PAN involves the medium blood vessels. Tr. at 173. The vessels in the kidneys are medium-sized. *Id.*

Dr. Alan I. Brenner, a rheumatologist, testified for respondent. Tr. at 176. His opinion is that petitioner had Wegener's which was an ongoing condition one year prior to her hepatitis B vaccinations. Tr. at 178. The symptoms of her Wegener's were otitis and mastoiditis. Tr. at 179. Dr. Brenner described Wegener's as "an inflammatory condition with two components." *Id.* Firstly, Wegener's causes granulomatosis inflammation in the upper airways and lungs. *Id.* Secondly, it causes small- and medium-sized vessel vasculitis, normally in association with glomerulonephritis. *Id.* Dr. Brenner stated he has had five Wegener's patients, two of whom had otitis media. *Id.* He opined that further evidence Ms. Schrum had Wegener's is her positive c-ANCA (seen in 90% of Wegener's patients), her untreatable otitis media which was not due to an infection, and her placement on corticosteroids. Tr. at 180-83.

Turning to the tissue overlap syndrome, Dr. Brenner stated that 10% of PAN patients are c-ANCA positive whereas 90% of Wegener's patients are c-ANCA positive. Tr. at 180,186. He further distinguished Wegener's patients from PAN patients by stating that the latter do not have upper airway problems. Tr. at 180. Because the mastoiditis does not come from an infection but is an inflammatory process, antibiotics will not cure it. Tr. at 181. Ms. Schrum's ear infection recurred in December 2002. Tr. at 182. She was noted on December 17, 2002 (Ex. 2, p. 68) to have right otitis media. Tr. at 183.

Dr. Brenner disputed Dr. Bellanti's testimony that Wegener's affects only the small vessels while PAN affects the middle-sized vessels, and includes the kidneys. Tr. at 184. He state d that there is a tremendous overlap in the size of the blood vessel involved. *Id.* Both Wegener's and microscopic PAN involve the kidneys. Tr. at 185. Dr. Brenner disagreed with Dr. Bellanti that these are immune complex diseases. Tr. at 187. He stated that they are immune

diseases. *Id.* They involve fixed antigen-antibody. *Id.* "Fixed" means antigen is on the cells. *Id.* These antigen-antibody reactions do not fix the components of the complement system. *Id.*

The ears are part of the upper respiratory system. Tr. at 193. The red blood casts detected in Ms. Schrum's urine are seen in Wegener's or microscopic PAN. *Id.* Her glomerular inflammation is consistent with either Wegener's or microscopic PAN. Tr. at 195. There is no glomerulonephritis in classic PAN. Tr. at 194, 233.

Dr. Brenner stated that the medical records in this case do not reflect reactions to the hepatitis B vaccinations. Tr. at 198. After Ms. Schrum's third hepatitis B vaccination on August 6, 2001, she had an x-ray of her left ankle on September 17, 2001. *Id.* Dr. Reddy did not write any clinical notes. Tr. at 199.

Dr. Brenner testified that Wegener's does not stay localized in the upper respiratory airways, but will progress, which is what happened to petitioner. Tr. at 200. There is no indication that vaccinations would aggravate Wegener's and, thus, the vaccinations were irrelevant to Ms. Schrum's course of disease. *Id.* Petitioner's treating rheumatologist Dr. Spalding missed that aneurysms occur in Wegener's and Wegener's is associated with otitis media with granulomatosis as its presenting symptom. Tr. at 203. When asked to explain why, if Ms. Schrum had Wegener's, she responded positively to the treatment she received for PAN, Dr. Brenner stated that one uses the same treatment for Wegener's and PAN, which is why Ms. Schrum improved. Tr. at 204.

Dr. Brenner stated we do not know the significance of antigenemia because microscopic polyangiitis or microscopic PAN is an immune disease and not an immune complex disease. Tr. at 205-06, 207. Dr. Brenner has never heard of hepatitis B vaccine causing Wegener's. Tr. at

210. Petitioner had an ongoing process. *Id.* Her sedimentation rate was normal as were her white blood cells. Tr. at 211. Ms. Schrum had destruction of tiny blood vessels, which explains her Raynaud's disease. Tr. at 217. Dr. Brenner does not know how Wegener's causes mastoiditis (granulomatous inflammation). Tr. at 226. Less than 10% of Wegener's patients have aneurysms on arteriograms. Dr. Brenner stated that if petitioner had any kind of PAN, it was microscopic PAN, not classic PAN, because the small blood vessels were involved. Tr. at 233.

DISCUSSION

Petitioner has the burden of proving that hepatitis B vaccine caused her condition, whether PAN (classic or microscopic) or Wegener's or a combination of the two. To satisfy her burden of proving causation in fact, petitioner must offer "(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, __ F.3d __, 2006 WL 560660, at *7 (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, supra, at *8; Althen, supra, 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, supra, 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 the injury, but also that the vaccine was a substantial factor in bringing about her injury. 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, supra, 418 F.3d at 1278; Grant, supra, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, supra, 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.

Id. at 549.

The Federal Circuit stated in Althen, supra, 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."

As the Federal Circuit stated in Knudsen, supra, 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, supra, at 1281 ("judging the merits of individual claims on a case-by-case basis").

The Federal Circuit in Knudsen, supra, at 549, also stated: "The special masters are not 'diagnosing' vaccine-related injuries." Yet, that is what the parties require the undersigned to do here. Did petitioner have Wegener's granulomatosis beginning one year before her three hepatitis B vaccinations and polyarteritis nodosa (PAN) after one or all of her vaccinations? Did she have microscopic PAN, but not classic PAN? Did she have both Wegener's and PAN, the first preceding the vaccinations and the second following? Did the natural course of her Wegener's lead to her symptoms subsequent to her chronic mastoiditis without the hepatitis B vaccinations having any effect, even though the natural hepatitis B infection is well-known to cause PAN, and one could reasonably conclude that already having a vasculitis made petitioner particularly vulnerable to developing another vasculitis after exposure to an antigen linked in numerous case reports to PAN?

The medical articles both parties have filed in this case show there can be an overlap of Wegener's and PAN. In those cases in which respondent's literature discusses a patient with Wegener's who also manifests aneurysms in his or her kidneys, that patient is diagnosed with both Wegener's and PAN. Because 10% of PAN patients and 90% of Wegener's patients have positive c-ANCA, the presence of c-ANCA in Ms. Schrum's case is not dispositive of whether she has Wegener's or PAN or both. What weighs most heavily in favor of Ms. Schrum's having Wegener's in 2000 is her chronic mastoiditis which never responded to multiple antibiotics. The conclusion that the cause of her mastoiditis was not infection is inescapable. Although her first treating otolaryngologist Dr. Dickinson says Ms. Schrum did not have Wegener's, Ms. Schrum's pathology results for September 16, 2000 show chronic inflammation and granulation tissue in the right mastoid. When Dr. Silverstein, her second otolaryngologist, did a subsequent mastoidectomy in April 2001, there were no granulomas.

The Federal Circuit emphasized taking the treating physicians' opinions seriously in Capizzano, supra, at *8. In Capizzano, the four treating physicians opined that hepatitis B vaccine caused Ms. Capizzano's rheumatoid arthritis. Here, none of Ms. Schrum's treating physicians opines that hepatitis B caused her PAN. They just insist she has PAN and not Wegener's. Dr. Spalding, petitioner's rheumatologist, expressly denied that petitioner had Wegener's, yet in the discharge summary he wrote on November 15, 2001 upon petitioner's release from Holmes Regional Medical Center, he stated "She has had a past history of an atypical granulomatous infectious process and treated by ear, nose and throat physician about a year ago and then finally stabilized." (Med. recs. at Ex. 3, p. 15.) Therefore, at one point of his analysis of Ms. Schrum's case, Dr. Spalding agreed at least that she had an atypical

granulomatous infectious process. Having granulomatous tissue could be consistent with Wegener's or an infectious process.

The literature respondent filed includes discussion of a limited form of Wegener's where the lungs are not involved. (Ms. Schrum did not have lung or sinus involvement.) Wegener's may present on rare occasions with just ear symptoms, according to the literature. It would be inappropriate to ignore the granulation tissue in Ms. Schrum's right mastoid in September 2000, as well as the stubbornly chronic mastoiditis she experienced for almost a year without improvement on multiple antibiotics and conclude her ear problem has no pathologic connection to her subsequent medical condition in 2001. Considering all the evidence in petitioner's medical records, the medical literature describing the limited form of Wegener's, and the testimony in this case, the undersigned holds that, based on Ms. Schrum's chronic mastoiditis where granulation tissue was found in the first of her two biopsies, that she had a limited form of Wegener's preceding vaccination and PAN, because of her kidney aneurysms, following vaccination.

The medical literature submitted states that vasculitides may occur in people susceptible to developing them. The next issue, then, is, considering that petitioner had a limited form of Wegener's before she received hepatitis B vaccinations, did her already having a vasculitis make her more susceptible to the effect of the hepatitis B vaccinations so that they caused her PAN, and thus, worsened her condition?

The medical literature shows and Dr. Bellanti testified that the natural infectious hepatitis B virus can and does cause PAN. People who experience PAN also experience antigenemia (antigens circulating in their blood). An interesting article which Dr. Bellanti emphasized in his

testimony and post-hearing report found antigenemia in hepatitis B vaccinees who did not have PAN. Since hepatitis B vaccine can cause antigenemia, and patients with PAN caused by the natural hepatitis B virus also have antigenemia, there seems to be a pathologic process traceable to the hepatitis B vaccine to explain how it can cause PAN in vaccinees. The undersigned is cognizant, however, of the discussion in the same article that surface antigen of hepatitis B may not play a role in PAN and that it could be some other antigen that underlies the biologic mechanism. Legally, petitioner does not have a burden to prove the specific biologic mechanism whereby hepatitis B vaccine can cause PAN. Knudsen, supra, at 549. By whatever specific biologic mechanism, natural hepatitis B infection causes PAN. Medical literature reveals numerous cases in which hepatitis B vaccine is suspected of causing PAN because of the appropriate temporal relationship and medically logical pathologic findings (although which one is the true mechanism is undiscovered so far).

Dr. Brenner raises the important point that Ms. Schrum's medical records are silent as to any reaction to her first two hepatitis B vaccinations, and rather general as to the third. Petitioner has filed unsworn statements from her friends and presumably her husband to support her assertions that she was unwell after each vaccination and worse after every succeeding dose. The Vaccine Act, 42 U.S.C. §300aa-13(a)(1), does not permit the undersigned to find in petitioner's favor based on her claims alone, unsubstantiated by medical records or by medical opinion. The only medical records are her DEXA or bone density test in May 2001 which notes that she had complained of lower back pain (her bone density was normal), and a September 2001 x-ray of her ankle because it was swollen and painful. The undersigned cannot conclude that this is a

positive rechallenge case because there are no medical records supporting petitioner's assertions of symptoms after the first and second hepatitis B vaccinations.

There is a history of symptomatology beginning in August which was the month that petitioner received her third hepatitis B vaccination. When petitioner saw Dr. Spalding on October 1, 2001, because Dr. Reddy referred her in September 2001 for polyarthralgia (many joint pains), Dr. Spalding took a history from her that two months earlier, she began experiencing pains in her knees and legs which had now spread to her arms. This is as near as the medical records come to there being any symptoms post-vaccination.

This is a close case because we have a petitioner with a pre-existing vasculitis (Wegener's) who received an antigen (hepatitis B vaccine) to prevent a disease that is well-known in its natural state to cause another vasculitis, PAN, and her symptomatology of PAN occurred within reasonable proximity to her third hepatitis B vaccination to suggest an immune process gone awry.

Dr. Brenner posits that Wegener's (restricted to the right ear) would naturally progress to include other parts of the body. But in the articles that respondent provided, those patients with Wegener's who had aneurysms in their kidneys were also diagnosed with PAN. From Dr. Brenner's testimony that Ms. Schrum's symptoms are consistent with microscopic PAN, the undersigned views that he would accept that her Wegener's could have included microscopic PAN, but that the vaccine had nothing to do with causing it.

Although classic Wegener's is often fatal, there is nothing to suggest that Ms. Schrum had classic Wegener's in 2000. As Dr. Dickinson states, if she had Wegener's (and the

undersigned assumes Dr. Dickinson is referring to the classic type), Ms. Schrum should have rapidly deteriorated and died.

The undersigned views Ms. Schrum as a ticking bomb in that her vulnerability to vasculitis was already apparent when she contracted a limited form of Wegener's the year before she received her hepatitis B vaccinations. Since the literature comments that those who are susceptible to vasculitis may contract PAN after hepatitis B vaccination, the undersigned believes this is what happened to Ms. Schrum. She was already experiencing a limited form of Wegener's with her chronic right mastoiditis starting in 2000. Her exposure to hepatitis B vaccine on three occasions in 2001 worsened her condition, leading to PAN, a different but related vasculitis. If not for the hepatitis B vaccinations, the undersigned does not believe Ms. Schrum would have had PAN.

One could analyze this case as significant aggravation of Ms. Schrum's pre-existing Wegener's, but the undersigned thinks the more applicable analysis comes from Shyface, supra. That Ms. Schrum developed Wegener's at all indicates that she is vulnerable to developing vasculitis. The undersigned holds that Wegener's was a substantial factor in continuing Ms. Schrum's vulnerability to develop vasculitis, and hepatitis B vaccine was a substantial factor which used Ms. Schrum's vulnerability to develop vasculitis to cause another related, but different, vasculitis (PAN). In legal terms, you take your victim as you find him.

The Federal Circuit has enjoined the special masters to rule in favor of petitioners in close cases. Capizzano, supra, at *8; Althen, supra, at 1280; Knudsen, supra, at 551. This is a close case and the undersigned rules for petitioner. Petitioner has proven that hepatitis B vaccine was a

substantial factor in causing her PAN and, but for hepatitis B vaccine, she would not have had PAN.

CONCLUSION

Petitioner is entitled to reasonable compensation. The undersigned hopes that the parties may reach an amicable settlement, and will convene a telephonic status conference soon to discuss how to proceed to resolve the issue of damages.

IT IS SO ORDERED.

_____ _____

DATE Laura D. Millman
Special Master