In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 12-254V
Filed: June 28, 2018
To Be Published

MARK MILES, legal representative of a minor child, J.M.,	*	
Petitioner,	*	
v.	*	Influenza ("flu") vaccine; significant aggravation of minimal change nephrotic syndrome; three strokes; timing of onset of second relapse.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

John F. McHugh, New York, NY, for petitioner.
Darryl R. Wishard, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

On April 18, 2012, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that influenza[2] ("flu") vaccine administered to his son J.M. on October 1, 2009 caused J.M. to have a second relapse of his preexisting nephrotic syndrome.[3] Pet. Preamble and ¶ 2.

[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 constitute a clearly unwarranted invasion of privacy. When such a decision is filed, petitioner has 14 days to identify and move to redact such information prior to the document's enclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall redact such material from public access.

[2] Influenza virus is "any of a group of orthomyxoviruses that cause influenza, including at least three genera: *Influenzavirus A, Influenzavirus B,* and *Influenzavirus C.* Antigenic variants are classified on the basis of their surface antigens (hemagglutinin and neuraminidase) as H1N1, H2N2, etc. Serotype A viruses are subject to major antigenic changes (antigenic shifts) as well as minor gradual antigenic changes (antigenic drift) and cause the major pandemics. Serotype B viruses appear to undergo only antigenic drift and cause more localized epidemics. Serotype C viruses appear to be antigenically stable and cause only sporadic disease." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 2062 (32nd ed. 2012) (hereinafter "Dorland's").

[3] Nephrotic syndrome is a "general name for any of a large group of diseases involving defective renal glomeruli, characterized by massive proteinuria and lipiduria with varying degrees of edema, hypoalbuminemia, and hyperlipidemia." Dorland's at 1840.

On August 6, 2012, petitioner filed a petition which should have been titled as an amended petition. It includes an extensive review of the medical records filed as of that date.

On October 23, 2012, petitioner filed a Supplemental Petition No. 2.

The parties attempted to settle this case but failed. The parties participated in mediation but mediation failed.

A hearing was held on October 17 and 18, 2017. Testifying for petitioner were petitioner, Dr. Albert Quan (J.M.'s treating pediatric nephrologist), and Dr. Joseph A. Bellanti (expert immunologist). Testifying for respondent were Dr. Bernard S. Kaplan (expert pediatric nephrologist) and Dr. Arnold I. Levinson (expert immunologist).

Petitioner filed his posthearing brief on December 22, 2017.

Respondent filed his posthearing brief on January 23, 2018.

Petitioner filed his reply brief on January 25, 2018.

FACTS

Prevaccination Records

J.M. was born on February 23, 2001. He is now 17 years old.

On April 19, 2001, when J.M. was two months old, his mother took him to Willow Bend Pediatric. J.M. had head congestion, was sneezing a lot, and had a loss of appetite. Med. recs. Ex. 1, at 43. He seemed sleepier than usual. Id. His head cold did not trigger minimal change nephrotic syndrome.

On April 24, 2001, J.M. received his first DTaP, Hib, hepatitis B, and IPV vaccines. Med. recs. Ex. 12, at 2. His first DTaP, Hib, hepatitis B, and IPV vaccinations did not trigger minimal change nephrotic syndrome.

On June 12, 2001, J.M. went to Willow Bend Pediatrics with congestion and a hoarse, rattling cough. Med. recs. Ex. 1, at 42. He had been fussy and up at night. He had eye drainage. He had a low-grade temperature of 99.2 degrees. Dr. Michael J. Frank diagnosed J.M. with bronchiolitis. Id. J.M.'s bronchiolitis did not trigger minimal change nephrotic syndrome.

On July 2, 2001, J.M. received his second DTaP, Hib, hepatitis B, and IPV vaccines. Med. recs. Ex. 12, at 2. His second DTaP, Hib, hepatitis B, and IPV vaccinations did not trigger minimal change nephrotic syndrome.

On February 9, 2002, J.M. was at Willow Bend Pediatrics because of congestion and cold symptoms plus loose stools. Med. recs. Ex. 1, at 41. Dr. Frank diagnosed J.M. with bilateral otitis media and bronchitis. Id. J.M.'s bilateral otitis media and bronchitis did not trigger minimal change nephrotic syndrome.

On March 26, 2002, J.M. saw Dr. Kimberly F. Mehendale at Willow Bend Pediatrics, with a history of cough and congestion for the prior two to three days. Id. Dr. Mehendale diagnosed J.M. with an upper respiratory infection ("URI"). Id. J.M.'s URI did not trigger minimal change nephrotic syndrome.

On April 16, 2002, J.M. received Varivax and Prevnar vaccinations at Willow Bend Pediatrics. Id. His Varivax and Prevnar vaccinations did not trigger minimal change nephrotic syndrome.

On May 24, 2002, J.M. received his third DTaP, Hib, hepatitis B, and IPV vaccines. Med. recs. Ex. 12, at 2. His third DTaP, Hib, hepatitis B, and IPV vaccinations did not trigger minimal change nephrotic syndrome.

On March 11, 2003, when J.M. was two years old, he went to Willow Bend Pediatrics with congestion for two days. Id. at 48. He had moderate nasal congestion. Dr. Susan J. Sickler diagnosed J.M. with an upper respiratory infection ("URI"). J.M.'s URI did not trigger minimal change nephrotic syndrome.

On October 6, 2004, when J.M. was three years old, he was supposed to receive flu vaccine, but because he had had a temperature of 101-103 degrees within the last 24 hours, the nurse at Willow Bend Pediatrics did not vaccinate him. Id. at 63. His febrile illness did not trigger minimal change nephrotic syndrome.

On December 24, 2004, J.M. went to Willow Bend Pediatrics and saw Dr. Mehendale, complaining of yellow runny nose for five days, green rhinorrhea, and congestion. Id. at 62. Dr. Mehendale wrote J.M. had green rhinorrhea and his symptoms were worsening. Id. J.M.'s respiratory infection did not trigger minimal change nephrotic syndrome.

On July 12, 2005, when J.M. was four years old, he went to Willow Bend Pediatrics with a urinary tract infection lasting two weeks with increased frequency. Id. at 61. Dr. Michael J. Frank diagnosed him with spastic bladder. Id. His urinary tract infection did not trigger minimal change nephrotic syndrome.

On August 8, 2005, J.M. went to Willow Bend Pediatrics and received DTaP, IPV, MMR, and his second hepatitis A vaccinations. Id. at 46. His DTaP, IPV, MMR, and hepatitis A vaccinations did not trigger minimal change nephrotic syndrome.

On November 20, 2006, J.M. received FluMist vaccine. Med. recs. Ex. 12, at 3. FluMist did not trigger minimal change nephrotic syndrome.

On August 31, 2007, when J.M. was six years old, he went to Willow Bend Pediatrics with puffy cheeks and eyes, and diarrhea. Med. recs. Ex. 1, at 60. He had mild suborbital edema and thin mucosa. Id. His infection did not trigger minimal change nephrotic syndrome.

On September 6, 2007, J.M. went to Children's Medical Center Dallas because he started having swelling of his body about 12 days previously. Med. recs. Ex. 1, at 279. The history was that J.M. had a new onset of edema, proteinuria, elevated creatinine, and hypoalbuminemia. Id. at 29. The findings on J.M.'s renal ultrasound were consistent with the typical findings seen in nephrotic syndrome, including large kidneys with increased echogenicity. Id. at 19-22. J.M. had acute renal injury with serum creatinine concentrations of 0.8 to 1.6 mg/dl (normal being 0.3-0.7 mg/dl). Med. recs. Ex. 2, at 15-22. J.M. was started on prednisone,[4] which he continued to take until February 4, 2008. Id. at 25-36.

On October 11, 2007, Dr. Mouin G. Seikaly, J.M.'s first pediatric nephrologist, noted J.M. had new-onset nephrotic syndrome, and a moderate amount of proteinuria. J.M. had not completed a full six weeks of daily steroid therapy. Id. at 28. On November 2, 2007, J.M. continued to have 30 mg/dl of proteinuria while on prednisone 40 mg every other day. Dr. Seikaly stated his concern that J.M. might relapse once prednisone was tapered. He noted he discussed with J.M.'s parents the use of Tacrolimus[5] and CellCept[6] therapy, and said J.M. would benefit from starting CellCept if he did not tolerate tapering off prednisone. Id. at 31.

On December 19, 2007, J.M. was in remission and his steroid was slowly tapered. Id. at 33. On February 6, 2008, J.M. was in remission and fully off prednisone. Id. at 35.

On January 15, 2008, J.M. went to Willow Bend Pediatrics with a stuffy nose and fatigue plus a fever of 101 degrees. Med. recs. Ex. 1, at 58. He had swollen mucosa, thick mucus, and a congested cough. Dr. Frank diagnosed J.M. with bronchitis. Id. J.M.'s bronchitis did not trigger a relapse of his nephrotic syndrome.

On March 26, 2008, J.M. was in remission, still off prednisone, but on Norvasc,[7] 5 mg

[4] Prednisone is "a synthetic glucocorticoid derived from cortisone, administered orally as an anti-inflammatory and immunosuppressant in a wide variety of disorders." Dorland's at 1509. Glucocorticoid is "any of the corticosteroids (steroids produced by the adrenal cortex) that regulate carbohydrate, lipid, and protein metabolism and inhibit the release of corticotropin. They also affect muscle tone and the microcirculation, participate in the maintenance of arterial blood pressure, increase gastric secretion, alter connective tissue response to injury, impede cartilage production, inhibit inflammatory, allergic, and immune responses, invoke shrinkage of lymphatic tissue, reduce the number of circulating lymphocytes, and affect the functions of the central nervous system. Some exert varying degrees of mineralocorticoid activity. In humans the most important ones are cortisol, cortisone, and corticosterone." Dorland's at 789.

[5] Tacrolimus is "a macrolide immunosuppressant of the calcineurin inhibitor group, derived from *Streptomyces tsukubasensis* and having actions similar to those of cyclosporine." Dorland's at 1868. Cyclosporine "acts by inhibiting activation of helper T lymphocytes." Id. at 456.

[6] CellCept is "trademark for preparations of mycophenolate mofetil." Dorland's at 325. Mycophenolate mofetil is "an immunosuppressive agent used in conjunction with cyclosporine and corticosteroids. . . ." Id. at 1216.

[7] Norvasc is "trademark for a preparation of amlodipine besylate." Dorland's at 1291. Amlodipine besylate is "a

twice daily. About that time, Norvasc was reduced and Cozaar[8] started. Med. recs. Ex. 19, at 2.

On July 28, 2008, when J.M. was seven years old, he went to Willow Bend Pediatrics. Med. recs. Ex. 1, at 45. Dr. Frank noted that J.M. was well, and J.M. received his second Varivax vaccination. His nephrotic syndrome was accompanied by persistent hypertension. Id. The second Varivax vaccination did not trigger a relapse of J.M.'s nephrotic syndrome.

On November 19, 2008, J.M. received flu vaccine. Med. recs. Ex. 1, at 3. No reaction was recorded. His flu vaccination did not trigger a relapse of his nephrotic syndrome.

On March 4, 2009, J.M. saw Dr. Seikaly who noted that J.M. had stayed well and did not have any swelling episodes and no complaints of headaches or dizziness. Med. recs. Ex. 16, at 12.

On June 15, 2009, Dr. Seikaly's nurse practitioner Becky Nolde-Hurlbert noted J.M. had **proteinuria since June 10, 2009**, swelling in his face and abdomen, and elevated blood pressure. J.M. **did not report any illness that could have triggered this first relapse of his disease** later characterized as recurrent nephrotic syndrome. Med. recs. Ex. 1, at 24-26, 36. J.M. had not been ill to trigger this relapse although he did have some allergy issues. Med. recs. Ex. 16, at 14.

On June 22, 2009, J.M.'s parents phoned Willow Bend Pediatrics to report that a week earlier, J.M. had a relapse of nephrotic syndrome and was back on high-dose steroids. Med. recs. Ex. 1, at 1.

By June 29, 2009, J.M. was in remission while taking another course of prednisone. On August 26, 2009, Dr. Seikaly noted that since J.M.'s last visit in March 2009, J.M. had not done well because he had a relapse in June, requiring steroid therapy. At the August 26, 2009 visit, J.M. was weaning off prednisone 25 mg every second day. He was also on Cozaar 25 mg daily. His urine protein was 1+. Med. recs. Ex. 10, at 77. J.M. was again weaned off prednisone by September 7, 2009. Med. recs. Ex. 16, at 14-16.

On August 17, 2009, J.M. went to Willow Bend Pediatrics for a physical examination. Med. recs. Ex. 1, at 34. He was noted to have had a relapse of nephrotic syndrome two months previously (June 2009). Id.

On August 26, 2009, J.M. saw Dr. Seikaly, who noted that since J.M.'s last visit in March 2009, he had not done well as he had a relapse in June 2009 which required steroid therapy. Id. at 32. J.M.'s last relapse was in February 2008. (This is the only mention in the medical records of a relapse in February 2008.) Id. Dr. Seikaly's plan was for J.M. to wean off steroids. Id. at 25. He recommended checking J.M.'s urine for protein with illnesses to detect relapses early. If

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calcium channel blocking agent used in the treatment of hypertension . . . ." Id. at 63.

[8] Cozaar is "trademark for a preparation of losartan potassium." Dorland's at 427. Losartan potassium is "an angiotensin II receptor antagonist, used as an antihypertensive. . . ." Id. at 1075.

proteinuria **or** edema returned, J.M.'s parents were to call the nephrology clinic. Id. He discussed J.M.'s receiving H_1N_1 and seasonal flu vaccines. Id. at 25-26.

Postvaccination Records

On October 1, 2009, at 4:00 p.m., J.M. received flu vaccine. Med. recs. Ex. 1, at 2 (a notation by J.M.'s pediatrician that he received "influenza (whole)"); Ex. 16, at 23. Entered on August 26, 2009 was a notation from Dr. Seikaly that J.M. has an unspecified disorder of immune mechanism. Med. recs. Ex. 16, at 22. This appears on the encounter date of October 1, 2009. Id.

On October 9, 2009, J.M. saw Dr. Seikaly, who noted J.M. had done well since his last visit in August 2009 until the past two weeks when he had an increase in his urine protein and developed edema. Med. recs. Ex. 10, at 72. The onset of J.M.'s increase in urine protein and development of edema would therefore have begun before his October 1, 2009 flu vaccination. However, petitioner's affidavit states that, prior to his October 1, 2009 flu vaccination, J.M.'s protein was negative for three weeks, but increased immediately and was markedly higher the morning after his flu vaccination. Ex. 5, at 1-1, § 3. J.M. had nearly completed a steroid taper (5 mg orally every 48 hours) from his relapse in June 2009. J.M. reported vomiting several times on October 13, 2009. He was hungry but unable to tolerate fluid or food. He did not have fever and had normal stools. Med. recs. Ex. 2, at 3.

On October 10, 2009, J.M.'s mother telephoned Willow Bend Pediatrics to ask if J.M. could receive flu shots since he was going on steroids. Med. recs. Ex. 1, at 4. The reply was that the flu shot was okay, but not Flu Mist. J.M.'s mother agreed. Id.

On November 4, 2009, J.M.'s urine protein stayed mildly elevated. He was again prescribed prednisone and weaned slowly. Id. at 9-10. When J.M. was weaned to 10 mg of prednisone every 48 hours in December 2009, J.M. had his third relapse. Id. at 12; Med. recs. Ex. 16, at 38. J.M. had his fourth relapse in March 2010. Med. recs. Ex. 7, at 1. He was weaned off steroids by April 20, 2010. Med. recs. Ex. 4, at 5.

On February 24, 2010, RN Nolde-Hurlbert noted it was difficult to determine the exact cause of J.M.'s relapse October 2009, but "anything that affects the immune system [ ] could be a contributing factor. No cause and effect relationship [between flu vaccine and nephrotic syndrome relapse] has been directly documented in the literature [;] there is only speculation." Med. recs. Ex. 16, at 42. Nurse Nolde-Hurlbert further noted, "In a child with Nephrotic Syndrome it is difficult to determine the exact cause of a relapse[.] Causes include but [are] not limited to: Spontaneous [ ] modulation of the immune system including infection. While the timing of the relapse is close to vaccine administration[,] no cause and effect relationship can be linked." Id. at 43.

On May 9, 2010, J.M. had his fifth relapse. Med. recs. Ex. 4, at 7.

On May 13, 2010, J.M. saw his second pediatric nephrologist, Dr. Albert Quan. Med. recs. Ex. 1, at 5. He recounts the history that J.M. had an initial onset of nephrotic syndrome in September 2007 when he was six years old. Id. He was given prednisone and went into remission. In June 2009, J.M. had his first relapse, was treated with prednisone again, and was weaned off prednisone in September 2009. In October 2009, J.M. had another relapse after flu vaccination. He was put back on prednisone and his urine protein became negative, but he was not weaned off until April 20, 2010. Id. His course was remarkable for persistent proteinuria and a prolonged course of prednisone. Id. J.M. was still on Cozaar. Id.

Although, on June 18, 2010, Dr. Quan recorded that J.M.'s first episode of nephrotic syndrome promptly responded to prednisone, J.M. actually did not respond for about six weeks. Id. at 4; see Med. recs. Ex. 2, at 33, 35. A renal biopsy did not show evidence of focal segmental glomerulosclerosis ("FSGS"). J.M. had one globally sclerosed glomerulus[9] out of a total of 25 glomeruli. Ultrastructural studies showed thin glomerular basement membranes. Med. recs. Ex. 4, at 35-36.

On June 25, 2010, Dr. Quan prescribed Prograf[10] for J.M. Med. recs. Ex. 3, at 2.

On January 26, 2011, Dr. Quan recorded that J.M. had not experienced proteinuria or edema since his office visit October 15, 2010. Id. Dr. Quan discussed the side effects of Prograf, including hypertension, tremors, and renal injury. Id. at 3. The plan was to wean J.M. off Prograf in the summer of 2011. Id. J.M.'s remission lasted 11 months while on Prograf. Ex. 5, at 2. Petitioner requested J.M.'s Prograf be discontinued to see how J.M. would respond because of petitioner's concern over the long-term effects of Prograf. Id. at 2-3.

By June 28, 2011, Dr. Quan noted J.M. had felt well since his last office visit and did not have any relapses. The plan was to stop Prograf in five days after weaning J.M.'s dosage. Id. at 16-17. J.M.'s Prograf was stopped. Dr. Quan recorded in his notes that J.M. should update all of his immunizations while he was off Prograf, stating J.M.'s October 2009 flu vaccination "may have triggered the onset of his nephrotic relapse." Med. recs. Ex. 12, at 74-81.

By the end of July, J.M.'s nephrotic syndrome relapsed and J.M. could not resume prednisone because his nephrotic syndrome did not respond any more to prednisone.

On August 18, 2011, J.M. had a cardiovascular attack ("CVA"). He was not on Prograf. Med. recs. Ex. 11. J.M. was admitted to Medical City Dallas Hospital. Id. at 73-80. J.M. suffered three strokes resulting in complete paralysis on his left side. Med. recs. Ex. 10 at 82; Ex. 5, at 3. He also had a syncopal episode while hospitalized, and was treated with anti-epileptic medications. Id. at 48, 51-52. He received inpatient and rehabilitation services until

[9] A renal glomerulus is "a globular tuft formed by capillaries in the kidney, the site of the filtration barrier between the blood and the kidney; it projects into the expanded end of a renal tubule, and together with its surrounding capsule (*glomerular capsule*) it constitutes a renal corpuscle." Dorland's at 787. "Sclerosed" means "hardened." Id. at 1680.

[10] Prograf is "trademark for preparations of tacrolimus . . . ." Dorland's at 1523. See n.4 supra for "tacrolimus."

September 23, 2011. Id. at 47-53.

J.M. continued to see Dr. Quan, as well as doctors specializing in neurology and hematology. In September 2011, Dr. Quan noted that J.M.'s CVA was secondary to his nephrotic relapse in July 2011. Med. recs. Ex. 14, at 1. J.M. continued weekly physical, occupational, and speech therapy. Id. at 4-9, 15-17. His hematologist noted in October 2011 that J.M. had made a remarkable recovery post-stroke, and recommended anticoagulation therapy for six months. Med. recs. Ex. 9, at 39-40. J.M.'s neurologist noted in October 2011 that J.M. could communicate verbally with normal speech and ambulate independently, but had residual left-sided weakness and concerns about mental processing speed. He had improving but residual left hemiparesis. J.M. continued on anti-epileptics. Med. recs. Ex. 9, at 5-6.

As of March 2012, J.M.'s neurologist recorded that J.M. was off steroids and continued taking antiepileptic medicine. Id. at 1-4. Dr. Quan noted that J.M. was receiving Prograf which would help prevent future strokes. Med. recs. Ex. 14, at 19. Based on a neuropsychological evaluation performed in June 2012, J.M. has cognitive deficits secondary to his CVAs. Med. recs. Ex. 13, at 16-24.

On October 20, 2015, J.M. saw Dr. Kazi Majeed, a pediatric neurologist. Med. recs. Ex. 63, at 36. He was last seen in 2012. J.M. had residual spastic hemiparesis. J.M. had a right cerebral infarct in August 2011. Tiny infarcts were also see in his left hemisphere. Testing for hypercoagulability showed factor V Leiden mutation.[11]

Expert Reports

Dr. Albert H. Quan

Dr. Albert H. Quan, J.M.'s second treating nephrologist, submitted his first expert report dated June 30, 2012. Ex. 7, at 1. In it, he gives a short summary of his medical qualifications (petitioner did not file Dr. Quan's C.V.). He has been board-certified in pediatric nephrology since 1993. He is licensed to practice in Texas. He was Associate Professor of Pediatrics at the University of Texas Southwestern Medical Center from 1993 to 2006. At the time of this letter, he was the Medical Director of Pediatric Nephrology and Pediatric Renal Transplantation at Medical City Children's Hospital and the Medical Director of Pediatric Dialysis at Home Kidney Care. Id. He became J.M.s' treating nephrologist in May 2010. He states he reviewed J.M.'s medical records and medical literature regarding nephrotic syndrome and vaccinations. Before he became J.M.'s pediatric nephrologist, J.M. was a patient of Children's Medical Center under Dr. Seikaly's care. Id.

Dr. Quan was under the mistaken impression that J.M. had received H_1N_1 flu vaccine instead of the trivalent seasonal flu vaccine. Id. (Petitioner filed a new report to replace this

[11] Factor V Leiden thrombophilia is an inherited disorder of blood clotting, i.e., an increased tendency to form abnormal blood clots that can block blood vessels. https://ghr nlm nih.gov/condition/factor-v-leiden-thrombophilia (last visited April 4, 2018).

report on April 4, 2013 as Ex. 20, minus Dr. Quan's initial reference to H_1N_1 flu vaccine.) On June 10, 2008, Dr. Quan did a kidney biopsy on J.M. which showed that J.M.'s nephrotic syndrome was due to minimal change[12] nephrotic syndrome ("MCNS"). Id. Dr. Quan explains nephrotic syndrome as a kidney disease that occurs when large amounts of protein are lost through urine (proteinuria), resulting in low blood protein levels (low serum albumin). Id. at 1-2. Low serum albumin causes edema or swelling throughout the body. Id. at 2. Dr. Quan says that the most common cause of nephrotic syndrome in children is MCNS. Id. While the exact mechanism is unknown, "loss of urinary protein in MCNS is thought to be due to immune system mediated injury to the kidney, which then results in massive losses of serum protein into the urine with resulting low serum albumin levels." Id. Dr. Quan supports this statement by noting: (1) nephrotic relapse usually occurs during or after a viral illness when immune system activity is markedly increased; (2) remission of nephrotic syndrome occurs with medicine that suppresses the immune system; (3) infusion of T-cell (a type of immune cell) proteins from patients with MCNS into normal mice induces nephrotic syndrome in them; (4) high levels of T-cell protein, interleukin 13, when infused into rats causes massive proteinuria; and (5) nephrotic syndrome can go into spontaneous remission during measles infection which is known to depress cell-mediated (T-cell) immunity. Id. Dr. Quan states that these observations taken together strongly support a role of the immune system in the development of nephrotic syndrome. Id.

Dr. Quan notes that, as early as the 1990s, case reports of nephrotic syndrome occurring after vaccinations were published. Id. Since vaccinations stimulate the immune system, Dr. Quan says it is plausible that such stimulation can lead to immune injury in the kidney followed by nephrotic relapses. Id. He notes in these reports that the time interval between various vaccinations and onset of nephrotic syndrome was consistent with an immune-system-mediated type of reaction, mentioning onsets of two weeks and six weeks post-vaccination. Id. (Both these intervals are far longer than the less than one day interval between J.M.'s vaccination and the increase in protein in his urine.)

Dr. Quan also notes that in all nephrotic syndrome cases, use of prednisone (which is the drug of choice for MCNS) was successful in treating the patients. Id. He admits that the risk of nephrotic relapses after vaccinations, while very plausible, remains somewhat controversial. Id. He states that very likely more study patients will be necessary to have the statistical power to detect an increased risk of relapses after vaccination. Id.

To Dr. Quan, J.M.'s relapse of nephrotic syndrome "virtually immediately" after his flu vaccination "strongly indicates a causal and temporal relationship" between vaccination and relapse. Id. Before his flu vaccination on October 1, 2009, J.M. was clearly in remission for about two months. He did not have a preceding viral illness and neither did his family. Id. Dr. Quan states the most likely triggering event for J.M.'s nephrotic relapse in October 2009 was the

[12] Minimal change disease is "subtle alterations in kidney function demonstrable by clinical albuminuria and the presence of lipid droplets in cells of the proximal tubules; abnormalities of foot processes of the glomerular epithelial cells are present but too subtle to be seen with light microscopy. It is seen primarily in children under age 6 but sometimes in adults with the nephrotic syndrome, and it may or may not progress to glomerulosclerosis or glomerulonephritis." Dorland's at 539.

preceding flu vaccination, where vaccine-induced immune stimulation led to immune injury to the kidney, followed by nephrotic syndrome. Id. at 3. He holds his opinion to a reasonable and substantial medical probability. Id. (Petitioner filed the same report as Ex. 18, titling it as an updated report, with no statement of a relapse in February 2008.)

Dr. Quan submitted his second expert report dated March 22, 2013. Ex. 21. He states that a majority of patients with nephrotic syndrome have one to two or more relapses per year and the frequency of such relapses decreases over time. Id. at 1. In more severe cases, patients develop steroid dependent nephrotic syndrome which results in a relapse when the patient stops taking steroids. In the most severe cases, patients develop steroid-resistant nephrotic syndrome where even high-dose steroids fail to treat the nephrotic syndrome. Id. Then more powerful immunosuppressive drugs such as Prograf, Ciclosporine, Cytoxan, or CellCept are used. Id.

Dr. Quan states that J.M.'s initial course was very favorable. Id. at 2. After he ceased taking steroids on January 28, 2008, his remission lasted over 18 months until his first relapse on June 10, 2009. Id. Steroid therapy for J.M.'s relapse was again successful and ceased on September 13, 2009. His infrequent relapse rate and excellent response to steroids strongly indicated his subsequent course would be uncomplicated with few relapses, if any. Id. After J.M.'s relapse, however, he developed steroid-dependent nephrotic syndrome which became steroid-resistant nephrotic syndrome, necessitating his taking Prograf for a year. Id. In August 2011, J.M. had another relapse of his nephrotic syndrome, followed by three cerebrovascular strokes, which Dr. Quan terms "a severe complication." Id. Dr. Quan does not explain how the 2011 relapse caused the three cerebrovascular strokes.

Dr. Quan states J.M.'s October 2009 relapse was diagnosed on the fourth day after he received flu vaccine. Id. He does not mention that J.M.'s onset was either the morning of the late afternoon vaccination on October 1, 2009, when he was five pounds heavier than on September 30, 2009, or that J.M.'s protein in his urine was detected on October 2, 2009 within 16 hours of his flu vaccination. What Dr. Quan does mention in his report is that case reports describing intervals between immunization and onset of nephrotic relapse show an onset as short as five days to as long as six weeks or more. Id. He does not mention that J.M.'s onset is too short to fit within the parameters in the case reports petitioner filed with Dr. Quan's report.

Dr. Quan goes on to describe a theory of how prior vaccinations can alter the immune system so that a subsequent vaccination can induce a relapse of nephrotic syndrome, citing the Islek[13] letter to the editor (which was also a reference in Dr. Quan's first report). In Islek, a four-year-old boy received hepatitis B vaccine on May 12, 1998, June 12, 1998, and November 12, 1998. He had nephrotic syndrome eight days after his third hepatitis B vaccination. Hepatitis B vaccine was identical in all three doses and those doses were administered one month apart between the first and second vaccinations, and five months apart between the second and third vaccinations. Dr. Quan uses Islek to buttress his opinion that J.M.'s prior flu vaccination on November 18, 2008, although it did not induce a nephrotic relapse, "likely further boosted his

[13] Nephrotic syndrome following hepatitis B vaccination by I. Islek, et al., 14 PEDIATR NEPHROL 89-90 (2004), describing a four-year-old boy whose eyelids swelled eight days after his third hepatitis B vaccination.

immunity and contributed to his vaccine induced relapse, similar to the hepatitis B induced relapse." Id. (Dr. Quan states it was November 18, 2008, but the informed consent form is signed November 19, 2008, Ex. 1, at 3, although there is a notation in a doctor's record for December 18, 2008 that flu vaccine was administered that day. Id. at 1).

However, there are discrepancies between the Islek letter to the editor and J.M.'s case. First, there is a gap of one year between J.M.'s 2008 and 2009 flu vaccinations unlike the intervals of months between hepatitis B vaccinations the child in the Islek letter to the editor received. Secondly, the contents of the 2008 and 2009 flu vaccines J.M. received were not identical, unlike the three hepatitis B vaccines the Islek child received. According to the Centers for Disease Control, the 2009-2010 flu vaccine contained a B/Brisbane/60/2008-like virus the 2008-2009 flu vaccine did not.[14] Therefore, Dr. Quan's attempt to link conceptually the experience of the Islek child with three successive, identical hepatitis B vaccinations administered months apart to J.M.'s receipt of two differing flu vaccines one year apart fails to prove his point that the effect of the prior 2008 flu vaccination was to boost J.M.'s immunity after the 2009 flu vaccination. Dr. Quan's statement that J.M. had "heightened immunity" because of the prior 2008 flu vaccination is not tenable based on the Islek letter to the editor. Id. at 3.

Since petitioner did not file Dr. Quan's C.V., there is no way to check his publications. However, at the hearing, respondent's counsel asked Dr. Quan if he ever published an article on minimal change nephrotic syndrome. Dr. Quan responded that he had not.

Dr. Bernard S. Kaplan

On June 18, 2013, Dr. Bernard S. Kaplan, respondent's expert pediatric nephrologist, wrote his expert report. Resp't's Ex. A. Dr. Kaplan was the Chief of Pediatric Nephrology at The Children's Hospital of Philadelphia ("CHOP") until he resigned in 2010. Id. at 1. He continues to work in the Division of Nephrology three days a week, seeing new and old patients. He is also Professor of Pediatrics and Medicine at The Perelman School of Medicine at the University of Pennsylvania. He is board-certified in pediatrics and in pediatric nephrology. He had been practicing pediatric nephrology for 35 years. He has studied and published papers and chapters on nephrotic syndrome and co-edited a textbook in which nephrotic syndrome and immunization of children with renal disease is discussed extensively. Dr. Kaplan has taught these subjects to medical students, interns, residents, and renal fellows at CHOP. Id.

[14] Respondent's Exhibit T shows that the November 19, 2008 trivalent flu vaccine J.M. received contained A/Brisbane/59/2007 (H_1N_1)-like virus; A/Brisbane/10/2007 (H_3N_2)-like virus; and B/Florida/4/2006-like virus (Med. recs. Ex. 1, at 3). Exhibit T shows that the October 1, 2009 trivalent flu vaccine J.M. received contained A/Brisbane/59/2007 (H_1N_1)-like virus; A/Brisbane/10/2007 (H_3N_2)-like virus; but the third component differed from the third component of the 2008 trivalent flu vaccine, containing B/Brisbane/60/2008-like virus (Med. recs. Ex. 16, at 23). Exhibit T also shows the components of the trivalent flu vaccines J.M. received on November 20, 2006. The flu vaccine contained A/New Caledonia/20/99 (H_1N_1)-like virus; A/Wisconsin/67/2005 ($H3N_2$)-like virus; and B/Malaysia/2506/2004-like virus (Med. recs. Ex. 12, at 3). Petitioner testified that J.M. did not receive flu vaccine in 2004 because he had had a fever within 24 hours of the proposed vaccination and the nurse cancelled the vaccination.

In summarizing J.M.'s medical records, Dr. Kaplan noted J.M.'s onset of nephrotic syndrome in September 2007, his first relapse in June 2009, his second relapse in October 2009, his third relapse in December 2009, his fourth relapse in March 2010, his fifth relapse in May 2010, and his sixth relapse in June 2011, followed by a cerebrovascular accident ("CVA") on August 18, 2011 while in relapse and off Prograf. Id. at 1-3. Dr. Kaplan notes that J.M. had idiopathic nephrotic syndrome as evidenced by edema, pleural effusions, proteinuria, and hypoalbuminemia at the age of six in September 2007. Id. at 3. He comments that this first episode resulted in acute renal failure with serum creatinine concentrations of 0.8 to 1.6 mg/dl. J.M.'s kidney function was initially below normal which Dr. Kaplan said is quite unusual for steroid-sensitive nephrotic syndrome at this state because the glomerular filtration rate is usually above normal. In addition, Dr. Kaplan states, not only did acute renal failure complicate J.M.'s initial course of nephrotic syndrome, but also J.M.'s first remission of nephrotic syndrome took longer than usual to achieve. This caused so much concern to Dr. Seikaly, J.M.'s first pediatric nephrologist, that he discussed using other agents to help induce a remission. Id. Dr. Kaplan notes that J.M. required anti-hypertensive therapy from the beginning which is also unusual for a patient with typical steroid-sensitive nephrotic syndrome. Id. To Dr. Kaplan, the factors of acute renal failure, prolonged period to achieve remission, and hypertension suggest that J.M.'s subsequent course of nephrotic syndrome might not be favorable. Id. at 4. Dr. Kaplan states this unfavorable course was borne out by J.M.'s subsequent relapses and his becoming less steroid sensitive. In addition, J.M. stayed in remission for almost a year on Prograf, but relapsed after discontinuing Prograf. A kidney biopsy did not show any evidence of immune deposits that might suggest J.M. had C1q nephropathy[15] or IgM nephropathy.[16] A CVA further complicated J.M.'s course, but he has not progressed to end-stage renal failure. Id.

Dr. Kaplan then defines idiopathic nephrotic syndrome, which is also called steroid-sensitive nephrotic syndrome or minimal change nephrotic syndrome. Id. The condition's characteristics are clinical and laboratory features of nephrotic syndrome, normal renal histology on light microscopy, no immunofluorescent deposits, and effacement of foot processes on electron microscopy. Nephrotic syndrome is almost always steroid sensitive, but in some cases may become resistant to steroids and thus require a calcineurin inhibitor or cyclophosphamide to induce and maintain a remission. About 30 percent of patients relapse after stopping calcineurin inhibitor and some have difficulty achieving subsequent remission with corticosteroids. Id. Dr. Kaplan states that predicting with any certainty a patient's long-term course with steroid-sensitive nephrotic syndrome is impossible. Constantinescu and his co-authors note that more

[15] C1q nephropathy is "a type of immune complex glomerulonephritis with deposits of complement component C1q; signs and symptoms are similar to those of minimal change disease or mild focal segmental glomerulosclerosis." Dorland's at 1242.

[16] IgM nephropathy is mesangial proliferative glomerulonephritis. Dorland's at 1242. Mesangial proliferative glomerulonephritis is "glomerulonephritis characterized by diffuse glomerular proliferation of mesangial and endocapillary cells and mesangial matrix, seen in patients with nephrotic syndrome; IgM deposits and complement 3 are often found in the mesangium." Id. at 786. The mesangium is "the thin membrane that helps support the capillary loops in a renal glomerulus." Id. at 1138. The renal glomerulus is "a globular tuft formed by capillaries in the kidney, the site of the filtration barrier between the blood and the kidney; it projects into the expanded end of a renal tubule, and together with its surrounding capsule . . . constitutes a renal corpuscle." Id. at 787.

than half of children with nephrotic syndrome have relapses which may be infrequent or frequent. Dr. Kaplan notes that J.M. took a long time to respond to prednisone after his diagnosis with nephrotic syndrome and also subsequently developed late steroid resistance. Id. He states that immunosuppressive treatment is a viable option in nephrotic syndrome patients who develop late steroid resistance. Id. at 5.

Dr. Kaplan states the etiology of idiopathic nephrotic syndrome is unknown. Medical literature does not report an association between relapse of idiopathic nephrotic syndrome and flu vaccine. Id. He states that scientific evidence does not exist to prove inactivated flu vaccine or any other vaccine causes or precipitates nephrotic syndrome or a relapse of nephrotic syndrome. He disputes the literature that Dr. Quan cites in his report. The Fernandes case report of an increase in proteinuria in an adult with steroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis differs from J.M.'s case because the Fernandes adult had preexisting proteinuria for six months, and it is unclear whether the H_1N_1 vaccine induced the increase. Id. Dr. Kaplan notes the Kimata case report of a five-year-old boy with idiopathic nephrotic syndrome who attained remission without steroid treatment in response to influenza B infection (not vaccination). Id. at 6. To Dr. Kaplan, the Kimata case report shows that any presumed association between flu vaccination and relapse of nephrotic syndrome is likely coincidental since the opposite (i.e., remission in the context of flu infection) may occur.

Dr. Kaplan states no evidence supports the assertion that flu vaccine alters the course of nephrotic syndrome, making it less sensitive to steroid therapy or subject to more frequent relapses or complications such as intravascular thrombi. He mentions the Zhu case control study showing flu vaccine was associated with a reduced risk of thrombotic embolism. Id. He discusses the Araya article which explores whether cytokines played a role in idiopathic minimal lesion nephrotic syndrome and concluded that evidence was lacking. Id. at 7. The theory was that T-cells increased glomerular permeability, but that was unproven. Then the theory was that activated T-cells released a circulating factor that caused idiopathic minimal lesion nephrotic syndrome and that resulted in no definitive conclusion. Thus, the pathogenetic cytokine has not been identified and there is doubt whether there is Th2 dominance in the disease. Id.

Dr. Kaplan states more recent studies question the mechanism for steroid induction of remission in idiopathic nephrotic syndrome. Id. Traditionally, the action of steroids was assumed to induce remission in idiopathic nephrotic syndrome by immune suppression. However, new studies by Clement show little is known about the mechanisms of steroids. Greenbaum and his co-authors state that evidence now indicates nephrotic syndrome results from podocyte[17] dysfunction. The use of conventional immunosuppressive agents (such as glucocorticoids and cyclosporine) which directly affect podocyte structure and function challenges the immune theory of T-cell-caused childhood nephrotic syndrome. Id.

[17] A podocyte is "a modified epithelial cell of the visceral layer of the glomerular capsule in the renal glomerulus; it has a small perikaryon and a number of primary and secondary footlike radiating processes (pedicels) that interdigitate with those of other podocytes and embrace the walls of glomerular capillaries." Dorland's at 1477. The perikaryon is "the cell body as distinguished from the nucleus and the processes. . . ." Id. at 1413.

Dr. Kaplan thinks the case reports on which Dr. Quan relies to support causation from vaccinations base their conclusions on pure coincidence. Id. at 8. Dr. Kaplan notes that J.M.'s pre-vaccination course was not uncomplicated. He initially had acute renal injury which is an uncommon occurrence in steroid-sensitive nephrotic syndrome. J.M.'s response to prednisone took a long time in his initial episode of nephrotic syndrome. He had a relapse before his October 1, 2009 flu vaccination. In addition, Dr. Seikaly treated him for hypertension. Dr. Seikaly was also concerned that J.M. might relapse once Dr. Seikaly tapered his prednisone. Dr. Seikaly's concerns were realized and contrast with Dr. Quan's statement in his report that J.M.'s subsequent course would be uncomplicated with few relapses if any. Id. Dr. Kaplan did not dispute that nephrotic syndrome often occurs in association with a viral illness, but he disputed that flu vaccine was a viral illness because it is an inactivated virus, i.e., a killed flu virus. He agrees that immunosuppressive agents do induce remissions but finds no connection to the idea that killed virus induces a relapse. Id.

Dr. Kaplan states the timing of relapses in idiopathic nephrotic syndrome is chaotic and unpredictable, occurring at any time with or without an antecedent viral infection. Id. He also states there is no scientific or published evidence supporting the view that a prior flu vaccination primes a recipient who has idiopathic nephrotic syndrome to have a relapse after a subsequent flu vaccination. Id. at 9. Thus, there is no evidence that J.M.'s 2008 flu vaccination together with his 2009 flu vaccination altered the course of his nephrotic syndrome. Lastly, Dr. Kaplan states there is no evidence that flu vaccine leads to CVA. Id.

Dr. Kaplan's C.V. shows, in addition to his professional responsibilities detailed in his expert report, that he was on the editorial board of Pediatric Nephrology from 1992-2012, and is a reviewer of the following journals: the Journal of the American Society of Nephrology, the Journal of Infectious Diseases, Mayo Clinic Proceedings, American Journal of Medical Genetics, American Journal of Kidney Diseases, Critical Care Medicine, Journal of Pediatrics, Clinical Pediatrics, Nephron (A Journal of Nephrology), New England Journal of Medicine, Pediatric Nephrology, Pediatric Emergency Care, Pediatrics, Developmental Pharmacology, Kidney International, the European Journal of Pediatrics, and Clinical Genetics. Ex. B, at 3. He has written 143 original papers as primary author or co-author. Id. at 6-15. He has written 92 chapters and reviews as primary author or co-author. Id. at 16-21. The topics of these papers, chapters, and reviews include nephrotic syndrome and minimal change nephrotic syndrome.

Dr. Arnold I. Levinson

Dr. Arnold I. Levinson, respondent's expert immunologist, submitted his first expert report dated October 28, 2013. Ex. D. He is board-certified in internal medicine and allergy and clinical immunology. Ex. D, at 1. Dr. Levinson states that bilateral pleural effusions[18] and ascites[19] complicated J.M.'s initial clinical course. Id. Dr. Levinson objects to Dr. Quan's opinion that flu vaccine caused J.M.'s October 2009 relapse because Dr. Quan did not explain

[18] Bilateral pleural effusions means "the presence of fluid in the pleural spaces" in both lungs. Dorland's at 596.
[19] Ascites is "effusion and accumulation of serous fluid in the abdominal cavity." Dorland's at 163. Serous fluid is "normal lymph of a serous cavity." Id. at 720.

how flu vaccine immunologically stimulated injury to J.M.'s kidneys, resulting in nephrosis. Id. at 5. Dr. Levinson does not accept the results of animal studies in humans with idiopathic minimal change nephrotic syndrome. Id. He states there is no credible evidence that any viral vaccination leads to a systemic immune response in test animals or in humans leading to a minimal change nephrotic syndrome-like disease. Id. at 5-6. He takes issue with Dr. Quan's equating the immune effect of three successive hepatitis B vaccinations with yearly flu vaccinations which "are changed year to year in anticipation of new viral epitopes that will be introduced into the community in each successive year." Id. at 6. With hepatitis B vaccinations, "each of the three vaccines contains the same viral proteins." Id. Thus, each successive hepatitis B vaccination provides a sequential boost to the recipient's immune response to hepatitis B virus. In contrast, there is "no a priori reason to expect increasing immune responses" to each successive year's flu vaccination. Id. Dr. Levinson concludes that J.M.'s October 1, 2009 flu vaccination neither caused nor significantly aggravated J.M's minimal change nephrotic syndrome, which relapsed on several occasions after its onset. Id. He also does not believe that J.M.'s flu vaccination on October 1, 2009 caused or significantly aggravated J.M.'s relapse in late July 2011.

Dr. Levinson's C.V. shows he is Emeritus Professor of Medicine and Neurology at the Perelman School of Medicine at The University of Pennsylvania School of Medicine. Ex. E, at 2. He used to be Chief of the Allergy and Immunology Section, Director of the Fellowship Training Program in Allergy and Immunology, and Director of the Center for Clinical Immunology. He currently serves as Associate Dean for Research. Id. at 1-2. He was author or co-author of 11 articles and 42 editorials, chapters, and invited journal reviews. Id. at 9-20.

Dr. Joseph A. Bellanti

Dr. Joseph A. Bellanti, petitioner's expert immunologist, submitted his first expert report dated June 3, 2014. Ex. 25, at 1. He agrees with Dr. Quan that nephrotic relapse often occurs after events such as viral illnesses and, more rarely, vaccinations. Id. at 2. He states every relapse of an immune-mediated condition like nephrotic syndrome can cause additional injury and lead to a course of illness that is more steroid-dependent and constantly relapsing. Id. at 3.

Dr. Bellanti considers J.M.'s third, fourth, and fifth relapses as continuations of his second relapse. His opinion is that the October 1, 2009 flu vaccine probably triggered J.M.'s sudden relapse of nephrotic syndrome. He finds it unsurprising that, having received two prior flu vaccinations (in 2006 and 2008), J.M.'s reaction to his 2009 flu vaccination was rapid. Dr. Bellanti's basis for his lack of surprise about the rapid onset on J.M.'s nephrotic syndrome is that J.M. had an anamnestic response to similar antigens due to prior priming or sensitizing J.M.'s memory cells. Id. Dr. Bellanti agrees with respondent's expert Dr. Kaplan that flu vaccine is not equivalent to a viral illness, but Dr. Bellanti writes flu vaccine is designed to present viral antigens to the immune system in a way similar enough to infection to cause the immune system to develop protective antibodies and T-memory cells as if the body confronted an infection. Dr. Bellanti states that it is generally understood that if an infection can trigger an immune-mediated condition, then vaccinations against those infections probably also can initiate a similar response

although far less frequently. Id. Dr. Bellanti says that the longer J.M. was in a state of disease instead of remission, the greater the likelihood of his developing thromboembolic complications. Id. Thus, his opinion is that flu vaccine triggered J.M.'s relapse, resulting in his subsequent strokes, and significant aggravation of his condition. He notes that receipt of prednisone and Prograf are also associated adversely with strokes. Id.

Dr. Bellanti's C.V. (Ex. 32) shows he is Director of the International Center for Interdisciplinary Studies of Immunology at Georgetown University and Professor of Pediatrics and Microbiology-Immunology School of Medicine at the same institution. Ex. 32, at 1. He lists 269 articles dating from 1961 to 2013 (Ex. 32, at 12-29), 200 abstracts dating from 1962 to 2008 (id. at 29-42), and 59 books or chapters in books dating from 1971 to 2012 (id. at 43-46).

Of his 269 articles from 1961 to 2013, Dr. Bellanti was co-author on just four articles having anything to do with the kidney, and only one of those four concerned minimal change nephrotic syndrome, which was published in 1981, i.e., 37 years ago.[20]

Of his 200 abstracts from 1962 to 2008, only one abstract concerned the kidney.[21]

Of his 59 books or chapters in books from 1971 to 2012, none concerns the kidneys (although some of the books have very general titles without specifying chapter content).

Dr. Kaplan's supplemental report

On July 17, 2014, Dr. Kaplan wrote a supplemental expert report in response to Dr. Bellanti's expert report. Ex. G. He comments that although Dr. Bellanti did not find a reference for a 1+ urine protein for J.M. on August 26, 2009, it is in Exhibit 10, at 3. Id. at 1. This would be 35 days before J.M. received flu vaccine on October 1, 2009. Dr. Kaplan contests Dr. Bellanti's statement that every relapse of an immune-mediated condition can cause additional injury. Id. at 2. Dr. Kaplan states that there is no evidence that every relapse of nephrotic syndrome can cause additional injury or result in more steroid dependency or become constantly relapsing. Moreover, there is no evidence that J.M.'s third, fourth, and fifth relapses were the

[20] Dr. Bellanti was third co-author of one article on acute kidney disease associated with prior streptococcal infection, resulting in reduction of serum hemolytic complement: Acute glomerulonephritis associated with normal serum ß$_1$C-globulin, by L.U. Tina, et al., 115 AM J DIS CHILD 1:29-36 (1968). He was fourth co-author of an article about abnormal microtubular structures in glomeruli and elevated serum-antibody levels in human diseases such as systemic lupus erythematosus and experimental viral infections: Glomerular microtubules of systemic lupus erythematosus, by T. Pincus, et al., 296 LANCET 7682:1058-61 (1970). He was fourth co-author of an article on minimal change nephrotic syndrome and immunological parameters: Studies of immunological parameters in minimal change nephrotic syndrome, L.U. Tina, et al., 46 ANN ALLERGY 1:34-36 (1981). He was sixth co-author of a two-part article on ataxia telangiectasia which can result in renal failure: Ataxia telangiectasia: immunologically mediated renal and hepatic failure, 55 ANN ALLERGY 4:539-40, 593-98 (1985). He was fourth co-author of an article on lack of graft rejection in a renal transplant AIDS patient: Lack of graft rejection in a renal transplant recipient with AIDS, J.E. Gootenberg, et al., 67 ANN ALLERGY 2:123-25 (1991).

[21] Dr. Theodore Pincus and Dr. Bellanti presented Anti-DNA antibodies and virus-like structures in the renal disease of systemic lupus erythematosus to the SOCIETY FOR PEDIATRIC RESEARCH, Atlantic City NJ, in May 1970. This was subsequently published in 4 PED RESEARCH 435 (1970).

result of the flu vaccination he received on October 1, 2009. Dr. Kaplan states these multiple relapses were from the disease process itself. Dr. Bellanti's idea that these relapses were really a continuation of J.M.'s second relapse makes no sense to Dr. Kaplan. Id.

Dr. Kaplan disagrees with Dr. Bellanti's opinion that J.M.'s immune system mounted a misdirected response to the vaccination that triggered a relapse of his nephrotic syndrome. Id. at 2-3. Dr. Kaplan calls this pure conjecture without any supporting evidence. He further disagrees with Dr. Bellanti that the longer J.M. was ill rather than in remission, the more likely he was to have thromboembolic complications. Id. at 3. Dr. Kaplan states the majority of nephrotic syndrome cases manifest thrombosis during the first flare or within six months after onset of the disease. Id. Contrary to Dr. Bellanti's statement, prednisone is no longer considered a predisposing factor in the development of thrombosis in nephrotic syndrome and there is no evidence showing Prograf causes cerebral thrombosis. Id. He agrees with Dr. Bellanti that any alleged relationship between flu vaccine and relapse of nephrotic syndrome is speculative and unproven. Id.

Dr. Levinson's supplemental report

On August 12, 2014, respondent's expert immunologist wrote a supplemental report in response to petitioner's expert immunologist Dr. Bellanti. Ex. J. Dr. Levinson states that a "major pillar" of Dr. Bellanti's opinion is that since a wild virus can cause an autoimmune disease, a viral vaccine can cause the same autoimmune disease. Id. at 1-2. The example upon which Dr. Bellanti relies is measles virus both in the wild and in the vaccine, but Dr. Levinson disputes the validity of this comparison, which Dr. Bellanti later admitted was a poor one. Id. at 2. First, measles vaccine contains live measles virus whereas flu vaccine is a killed virus vaccine. Id. Therefore, it is impossible that live influenza virus infected any of J.M.'s body tissues as could measles virus. Moreover, there is no evidence that flu virus infects any part of the kidney, which is the target of tissue injury in minimal change nephrotic syndrome. Id. Measles virus, on the other hand, can infect neurons and other cells within the brains of patients who develop encephalitis. In addition, medical articles do not show that any wild flu virus components share molecular motifs that the kidney expresses. Id. Dr. Bellanti posits J.M. had a misdirected response, but Dr. Levinson says Dr. Bellanti did not show a misdirected response occurred or resulted in J.M.'s relapse of nephrotic syndrome. Id. at 2-3.

Secondly, Dr. Bellanti attributes a less than 24-hour development of relapse of nephrotic syndrome after J.M. received flu vaccine on October 1, 2009 to an anamnestic response, but Dr. Levinson asks to what did an anamnestic immune response respond. Id. at 3. Dr. Levinson states Dr. Bellanti's arguments lack substance. Id.

Dr. Bellanti's supplemental report

Dr. Bellanti submitted his supplemental report dated October 10, 2014. Ex. 28. He reviewed the reports respondent's experts Dr. Kaplan and Dr. Levinson wrote. Dr. Bellanti agrees with respondent's experts that Dr. Bellanti's explication in his initial written opinion of a

causative relationship between measles virus and encephalitis and between measles vaccine and encephalitis was not (as Dr. Bellanti put it) "an ideal choice for an example" because measles vaccine is an attenuated viral vaccine, whereas flu vaccine (the vaccine in J.M.'s case) is a killed virus vaccine. Id. at 1. But Dr. Bellanti still adheres to the belief that the known effects of natural disease are relevant in evaluating what a vaccine can theoretically cause. Id. He cites the Institute of Medicine ("IOM") publication, ADVERSE EVENTS ASSOCIATED WITH CHILDHOOD VACCINES: EVIDENCE BEARING ON CAUSALITY 28 (K.R. Stratton, et al., eds., National Academy Press 1994), for the same point. Id. at 2.

Dr. Bellanti then uses what he describes as a better example than measles virus and measles vaccine for the principle that, since viruses cause disease, viral vaccines can cause the same disease: influenza and upper respiratory infections can cause or trigger Guillain-Barré syndrome ("GBS"); therefore, flu vaccine can also cause GBS. Id. Dr. Bellanti states he agrees with Dr. Kaplan that a viral illness such as influenza can trigger nephrotic syndrome ("and logically can also trigger a relapse of nephrotic syndrome."). Id. He ties J.M.'s third, fourth, and fifth relapses to his second relapse on the basis that weaning J.M. off steroids became impossible after the second relapse. Id. at 3. Dr. Bellanti identifies the timing of J.M.'s second relapse as the day after his flu vaccination on October 1, 2009. Id. Dr. Bellanti states he suspects that the immune-mediated reaction involved both the innate and adaptive immune systems. Id.

Dr. Quan's supplemental report

On January 2, 2015, Dr. Quan wrote a supplemental expert report in response to respondent's expert nephrologist Dr. Bernard Kaplan. Ex. 40. Dr. Quan begins by giving a timeline of events. For October 1, 2009, he states that J.M. received flu vaccine and, four to five days later, he experienced his second nephrotic relapse. Id. at 1. (This is not accurate.) After resuming prednisone, J.M. was put on Prograf until mid-June 2011. By August 2011, J.M. had his third nephrotic relapse. Id. After J.M.'s CVA, he restarted prednisone and Prograf and went into remission two weeks later. Id. at 2. Dr. Quan states that J.M. remains in remission on both medications. Id. Dr. Quan relates J.M.'s steroid dependence, third nephrotic relapse and CVA to his flu vaccination. Id.

Dr. Quan disagrees with Dr. Kaplan's opinion that J.M. had third, fourth, fifth, and sixth relapses. Dr. Quan's opinion is that J.M. never truly went into remission after his 2009 flu vaccination. Id. He also disagrees with Dr. Kaplan that an elevation in serum creatinine from 0.8 to 1.6 mg/dl was indicative of acute renal failure. Id. Dr. Quan attributes J.M.'s elevation of creatinine to mild dehydration due to a concurrent viral illness and lower blood volume due to low blood albumin level. Id. Dr. Quan opines that 10 percent or more of children can take up to six to eight weeks of prednisone before going into remission, as J.M. did. J.M.'s disease was steroid sensitive and, thus, Dr. Quan concludes that J.M.'s early disease course did not indicate poor outcome. Id.

Finally, Dr. Quan reviews Dr. Kaplan's statement that current thinking on the pathogenesis of minimal change nephrotic syndrome may have changed and now focuses on

non-immune etiologies. Id. Dr. Quan admits that some new studies do indeed indicate other possible mechanisms leading to nephrotic syndrome, particularly involving the podocyte, a cell central to the glomerular basement membrane, which is the filter of the kidney. He gives an example of high levels of a podocyte-secreted protein (ANGPTL4) within the podocyte (versus in circulation) can lead to nephrotic syndrome, citing Jiang. (Petitioner filed the Jiang article as Exhibit 49. It is mostly in Mandarin with an abstract in English.)

Dr. Quan says many studies continue to implicate a role for the immune system in the development of nephrotic syndrome, e.g., elevation of lymphokine interleukin-13 in CD-4 and CD-8 T-cells during a nephrotic relapse and reduction of interleukin after prednisone therapy. In an animal study, researchers induced loss of urinary protein in mice by injecting CD 34+ T-cells into them, which Dr. Quan finds consistent with a role for immature immune cells in the development of nephrotic syndrome.

Dr. Quan concludes his supplemental report by asking:

> So, where does the truth about the cause of minimal change nephrotic syndrome lie? Does the immune system play a major role or can this role be relegated to other causes? The actual truth may lie in the fact that nephrotic syndrome may have different underlying causes in different patients. Newer mechanisms of nephrotic syndrome, therefore[,] do not preclude an important role for the immune system in many patients. However, such differences in the underlying causes to the nephrotic syndrome may explain why a "one size fits all" conventional treatment regimen is not effective in all patients.

Id. at 3.

Dr. Quan concludes that J.M. was in the low-risk category of minimal change nephrotic syndrome before his 2009 flu vaccination which abruptly and severely altered his nephrotic syndrome. Id. at 3-4. He attributes J.M.'s CVA to hypercoagulability (increased risk of development of blood clots), which is a well-known complication of nephrotic syndrome. Id. at 4. He states that hypercoagulability results in urinary loss of clotting proteins which leads to a risk of inappropriate formation of blood clots. He also states it is biologically plausible that a vaccine adverse event can cause a more severe nephrotic syndrome leading to a CVA. Id.

Dr. Quan quotes from Dr. Bellanti's expert report that "'if a viral infection [such as influenzae] can trigger an immune mediated condition [such as nephrotic syndrome], then the vaccine [influenza immunization] for those infections are [sic] probably also capable of initiating a similar deleterious response [nephrotic syndrome].'" Id.

Dr. Kaplan's supplemental report

On September 21, 2015, Dr. Kaplan wrote a supplemental report in response to Dr. Bellanti's October 10, 2014 expert report and Dr. Quan's January 2, 2015 expert report. Ex. L. Dr. Kaplan states "there is absolutely no evidence that influenza or influenza vaccine induce[s] nephrotic syndrome." Id. at 1. He quotes Dr. Bellanti's statement that any alleged relationship between flu vaccine and relapse of nephrotic syndrome is "speculative and unproved." Id. Dr. Bellanti also wrote that the definition of a medical theory is that it is speculative and unproved. Id.

Dr. Kaplan finds it inconceivable that flu vaccine caused J.M.'s episode of venous thrombosis several years later, as Dr. Quan suggests in his report. Id. Dr. Kaplan notes that although J.M.'s nephrotic syndrome course changed after flu vaccination on October 1, 2009, J.M. did subsequently enter full remission. Id. at 4. Dr. Kaplan states there is no evidence that flu vaccine altered J.M.'s course as this pattern occurs in patients who were previously sensitive to steroid treatment. Id. Dr. Kaplan disagrees with Dr. Quan's assertion that J.M. did not have acute renal failure during his initial presentation of nephrotic syndrome. He calls Dr. Quan's attention to the KDQUO Guidelines on Acute Renal Injury,[22] pointing out that even mild, reversible acute kidney injury ("AKI") has important clinical consequences including increased risk of death. Id. Contrary to Dr. Quan's opinion, Dr. Kaplan notes that the medical records prove that J.M.'s elevation in serum creatinine from 0.8 to 1.6 mg/dl constitutes acute renal failure. J.M. took longer than usual to achieve his first remission (which occurred before the flu vaccination at issue). Id.

Dr. Kaplan notes that J.M.'s time to respond to prednisone differed from 90 percent of patients with nephrotic syndrome. Id. According to the Siegel[23] article, if someone does not relapse within three years of onset of nephrotic syndrome, his prognosis is good. But J.M. had two relapses within three years of his initial episode. Therefore, complete resolution was unlikely. Even after 15 years post-onset, 20 percent of relapsing patients continue to have relapses, according to Siegel. Id.

Dr. Kaplan cites the conclusion of the Kim[24] article that a higher incidence of initial and subsequent steroid resistance in minimal change nephrotic syndrome suggests the syndrome may not be as benign as earlier studies indicate. Id. Dr. Kaplan adds that J.M. was at increased risk for relapses because early indicators in his course showed his prognosis might be poorer. Id. at 4-5. Dr. Kaplan clarifies his statement denying a medical literature association of flu vaccine and idiopathic nephrotic syndrome by stating no report in the world literature describes an association between minimal change nephrotic syndrome and flu vaccine in children. Id. at 5. Dr. Kaplan states the problem with describing a supposed pathogenesis of minimal change nephrotic syndrome is that it involves speculation. No pathogenetic evidence or epidemiological

[22] Kidney Disease: Improving Global Outcomes (KDIGO), Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2 KIDNEY INTER SUPP 1-138 (2012). Ex. Q.
[23] Long-term follow-up of children with steroid-responsive nephrotic syndrome, by N.J. Siegel, et al., 81 J PEDIATR 2:251-58 (1972). Ex. R.
[24] High incidence of initial and late steroid resistance in childhood nephrotic syndrome, by J.S. Kim, et al., 68 KIDNEY INTER 1275-81 (2005). Ex. S.

support links flu vaccine to relapses of minimal change nephrotic syndrome, subsequent steroid resistance, or venous thrombosis. Id. Dr. Kaplan emphasizes Dr. Quan's admission that the truth about the cause of minimal change nephrotic syndrome is unknown, by quoting Dr. Quan's statement in Exhibit 40, at 3, that "nephrotic syndrome may have different underlying causes in different patients." Id.

Dr. Kaplan concludes that before J.M. received flu vaccine on October 1, 2009, he had acute renal failure, responded late to steroid therapy, and had two relapses (the first on June 10, 2009, the second around the time of the October 1, 2009 flu vaccination) within three years of the onset of his minimal change nephrotic syndrome on September 6, 2007, putting J.M. in a high-risk category. Id. After his second nephrotic relapse, J.M.'s clinical course was "abruptly and severely altered." Id. After J.M.'s second relapse, he became steroid-dependent and remained on steroids continuously for eight months until June 20, 2010 when he went on Prograf to which he responded. Id. But, Dr. Kaplan says evidence is lacking that flu vaccine either caused this second relapse or altered the course of J.M.'s minimal change nephrotic syndrome. Id. He cites the Kim article stating, "An important new finding in our study was the surprisingly high number of patients who developed late steroid resistance during subsequent relapses despite being initially steroid responsive." Id. at 5-6.

Dr. Kaplan continues in his conclusion that when in June 2011, J.M. was weaned off Prograf, he had his third nephrotic relapse, followed two months later in August 2011 by his cerebrovascular accident. Id. at 6. Dr. Kaplan attributes the cause of J.M.'s CVA to hypercoagulability (increased risk of development of blood clots due to urinary loss of clotting proteins), which is a well-known complication of nephrotic syndrome. Dr. Kaplan states there is absolutely no plausible link between J.M.'s second relapse and the thrombosis following his last relapse. Id.

Articles

Among the medical articles petitioner filed to which Dr. Quan referred in his initial expert report (Ex. # 7) was a Letter to the Editor entitled Nephrotic syndrome following hepatitis B vaccination, by I. Islek, et al., 14 PEDIATR NEPHROL 89-90 (2004), describing a four-year-old boy whose eyelids swelled **eight days** after his third hepatitis B vaccination. Id. Although the authors admit that causal relationship between minimal change nephrotic syndrome and hepatitis B vaccine is not easily established and the development of minimal change nephrotic syndrome after hepatitis B vaccination might be coincidental in this case, the timing of minimal change nephrotic syndrome after hepatitis B vaccination in this case strongly favored an immune-mediated side effect of vaccination. Id. This eight-day interval between vaccination and swelling contrasts with J.M.'s onset of increased protein within 16 hours of his October 1, 2009 flu vaccination and with the onset of edema the same day as his October 1, 2009 flu vaccination.

Another of petitioner's filings was one of Dr. Quan's references in his initial expert report (Ex. # 7), a case report entitled Minimal change nephrotic syndrome in an 82 year old patient following a tetanus-diphtheria-poliomyelitis-vaccination, by C. Clajus, et al., 10 BMC

NEPHROL 21-25 (2009). (Respondent also filed this as Ex. C, Tab 4.) The onset interval between Td/polio (REVAXIS) vaccination and edema was **four weeks**. Id. at 22. The authors state that the clinical findings and course of minimal change nephrotic syndrome in this 82-year-old female patient were typical for the disease. Id. at 23. The authors recount other articles in which a vaccine recipient had minimal change nephrotic syndrome. A woman suffered the syndrome 10 days after smallpox vaccination. Id. They report a woman who had minimal change nephrotic syndrome four months after pneumococcal vaccination. Id. They report a woman who had minimal change nephrotic syndrome four days after flu vaccination. Id. They report a three-year-old boy who had minimal change nephrotic syndrome 17 days after hepatitis B vaccination. Id. They report a four-year-old boy who had minimal change nephrotic syndrome eight days after hepatitis B vaccination. These intervals contrast markedly with J.M.'s increased protein within 16 hours of flu vaccination. The authors note the variety of time intervals in these case reports, stating:

> The time until the onset of symptoms varies in all described cases from days to months, which could be explained by the different time it took for the respective vaccine to trigger an immune response. Nephrotic syndrome occurred after the second administration of the vaccine which suggests that the last administration has boosted a pre-existing immune response from the first vaccination.

Id. at 24.

Another of petitioner's filings of Dr. Quan's references in his initial expert report (Ex. # 7) and in his supplemental expert report (Ex. # 40) as Exhibit 45 was a case report including one of a man who developed Guillain-Barré syndrome ("GBS") and nephrotic syndrome, the former within **two weeks** of flu vaccination, and the latter within three weeks of flu vaccination. Dr. Bellanti also referred to this case report as Exhibit 31 in his supplementary report (Ex. # 28). Respondent's expert Dr. Kaplan referred to this case report as Exhibit, Tab 5, in his expert report: Guillain-Barré syndrome coexisting with pericarditis or nephrotic syndrome after influenza vaccination, by C-D Kao, et al., 106 CLIN NEUROL NEUROSURG 136-38 (2004). The authors emphasized the three-week onset of nephrotic syndrome after flu vaccination as creating suspicion of a causal relationship. Id. at 137. This three-week interval contrasts with J.M.'s onset of increased protein within one-half day of vaccination.

One of Dr. Quan's references in his second expert report (Ex. # 21) was a case report involving a 61-year-old woman who received haemophilus influenzae type B ("HiB"), diphtheria-tetanus toxoid ("Dt"), and PPV 23 (pneumococcal or Pneumovax) vaccinations one year after having a stem-cell transplant for acute myelogenous leukemia. She had progressive weight gain, edema and fatigue **five days** after immunization. Fourteen days after immunization, she had anasarca[25] and was discovered to have acute renal failure and nephrotic proteinuria: Minimal-change nephrotic syndrome in a hematopoietic stem-cell transplant recipient, by B.D.

[25] Anasarca is "generalized massive edema." Dorland's at 75.

Humphreys, et al., 2 NATURE CLIN PRACTICE NEPHROL 9:535-39 (2006). The undersigned notes that this woman's edema preceded her proteinuria. The woman in the case report was diagnosed with minimal change disease ("MCD"). Id. at 536. The authors list immunization as one of the causes of MCD. Id. at 538. They note that case reports have linked MCD to influenza, pneumococcal, and hepatitis B vaccines. Id. at 537. They associate the woman's MCD to "an allergic reaction to vaccination." Id. They say, "We speculate that vaccination itself triggered the hypersensitivity reaction." Id. The authors found significant to their speculation the five-day onset between the woman's three vaccinations and her MCD. Id. Since the woman was a recovering cancer patient, the authors "propose that simultaneous immunization with three different vaccines might have resulted in hyperstimulation of the recovering immune system, leading to dysregulated T-lymphocyte activation and, subsequently, MCD." Id. However, the authors also say, "we cannot rule out the possibility that the association between vaccination and MCD is co-incidental, because all HSCT [hematopoietic stem-cell transplant] recipients receive immunizations after successful engraftment and, to our knowledge, no other case of MCD has been reported in this context." Id. at 538. This 14-day interval until the patient had proteinuria contrasts with J.M.'s 16-hour interval after vaccination.

Petitioner filed as Exhibit 27, an article entitled Cerebral sinovenous thrombosis and idiopathic nephrotic syndrome in childhood: report of four new cases and review of the literature, by J. Fluss, et al., 165 EUR J PEDIATR 709-16 (2006). The authors state nephrotic syndrome is a common renal disorder in children characterized by severe proteinuria, hypoalbuminemia, and edema. Id. at 709. Most childhood nephrotic syndrome is attributable to minimal change glomerulopathy. Id. Nephrotic syndrome is associated with a hypercoagulable state and thrombosis in both children and adults. Id. The hypercoagulable state is due to urinary loss of anticoagulants, increased platelet aggregability, and intravascular volume depletion. Id. at 709-10. Thrombosis is either venous or, less commonly, arterial and may be more frequently associated with steroid-resistant nephrotic syndrome. Id. at 710. The authors note that cerebral sinovenous thrombosis is infrequent in nephrotic children, whereas renal vein thrombosis is the common site of thrombosis. Id.

Petitioner filed as Exhibits 30 and 44 a Letter to the Editor to which Dr. Quan referred in his supplemental report (Ex. # 40). Dr. Bellanti also referred to this Letter to the Editor as Exhibit 30 in his supplementary report (Ex. # 28). Respondent also filed it as Exhibit N: Minimal change disease following influenza vaccination and acute renal failure: just a coincidence?, by S. Gutiérrez, et al., 32 NEFROLOGIA (MADR.) 3:414-15 (2012). A 44-year-old man received flu vaccine and, **18 days later**, had edema in his face and legs, and cervical lymphadenopathy. Id. at 415. Renal biopsy showed severe acute tubular injury. Id. The authors posit various theories of how minimal change disease occurs. Id. at 415. They conclude that the immune response after flu vaccine generated MCD possibly due to hypersensitivity syndrome while admitting the pathogenic bases are still controversial and debatable. Id. This 18-day interval until the patient had edema and lymphadenopathy contrasts with J.M.'s 16-hour interval after vaccination for proteinuria.

Petitioner filed as Exhibit 41 an article to which Dr. Quan referred in his supplemental

report (Ex. # 40): Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms, by J.G. Vande Walle, et al., 346 LANCET 148-52 (1995). The authors note three different presentations in early relapse of minimal change nephrotic syndrome in children. The first presentation occurred in children who already showed sodium retention before they manifested overt hypoproteinemia. Id. at 151. They already showed sodium retention while renal plasma flow was high. This finding supported the idea that an intrarenal defect is involved in sodium retention in minimal change nephrotic syndrome children as well as in adults. Id. They opined that nephrotic edema cannot be explained solely by hypovolemia.[26] "In all cases, sodium retention has a primary renal component, and may precede overt hypoproteinaemia." Id.

Petitioner filed as Exhibit 42 a report from The International Study of Kidney Disease in Children to which Dr. Quan referred in his supplemental report (Ex. # 40): The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone, 98 J PED 4:561-64 (1981). The authors looked at response or nonresponse during eight weeks of steroid treatment of minimal change nephrotic syndrome. Id. at 564. Almost 94 percent of those who responded to steroid treatment had already responded to steroid treatment by four weeks.

Petitioner filed as Exhibit 43 a case report to which Dr. Quan referred in his supplemental report (Ex. # 40): Minimal change nephrotic syndrome in a 65-year-old patient following influenza vaccination, by J.T. Kielstein, et al., 54 CLIN NEPHROLOGY 3:246-48 (2000). A 65-year-old woman received flu vaccine on January 13, 1999. Six to eight hours later, she had a cough, severe headaches and left-sided ear aches. **Four days later**, she had leg edema, weight gain, and hypertension. Lab evaluation showed hypoproteinemia. Id. at 246. The authors thought this case illustrated a potential way in which stimulation of the immune system may relate to the manifestation of MCNS. Id. at 248. The four-day interval contrasts with J.M.'s 16-hour interval after vaccination. Id.

Petitioner filed as Exhibit 46 a Letter to the Editor to which Dr. Quan referred in his supplemental expert report (Ex. # 40). Dr. Bellanti also referred to this Letter to the Editor as Exhibit 29 in his supplementary report (Ex. # 28). Respondent filed this as Ex. C, Tab 3, after Dr. Kaplan's expert report (Ex. C) and as Ex. M after Dr. Kaplan's supplemental report (Ex. L): Relapse of Nephrotic Syndrome Following the Use of 2009 Influenza A (H1N1) Vaccine, by P. Fernandes, et al., 56 AMER J OF KIDNEY DIS 1:185-86 (2010). A 50 year-old woman with steroid-resistant nephrotic syndrome received H_1N_1 vaccine and, **one week later**, had a relapse of her nephrotic syndrome. Id. at 185. The authors regarded her relapse as an adverse reaction to the H_1N_1 vaccine. Id. This one-week interval contrasts with J.M.'s 16-hour interval after vaccination.

Petitioner filed as Exhibit 47 an article to which Dr. Quan referred in his supplemental expert report (Ex. # 40): Podocyte secreted Angiopoietin-like 4 mediates proteinuria in glucocorticoid sensitive nephrotic syndrome, by L.C. Clement, et al., 17 NAT MED 1:117-22

[26] Hypovolemia is "abnormally decreased volume of circulating blood in the body. . . ." Dorland's at 908.

(2011). The authors state the major manifestations of nephrotic syndrome include proteinuria, hypoalbuminemia, edema, hyperlipidemia, and lipiduria. Id. at 117. Minimal change disease is usually glucocorticoid sensitive. The authors state, "Despite recent identification of key structural proteins in the glomerular capillary loop, many disease mechanisms in nephrotic syndrome remain unresolved." Id.

Petitioner filed as Exhibit 48 an article to which Dr. Quan referred in his supplemental expert report (Ex. # 40): Th1 and Th2 Cytokine mRNA Profiles in Childhood Nephrotic Syndrome: Evidence for Increased IL-13 mRNA Expression in Relapse, by H-K Yap, et al., 10 J AM SOC NEPHROL 529-37 (1999). The authors state the "current understanding" (this article is 19 years old) of the pathogenesis of idiopathic nephrotic syndrome of childhood is probably due to a primary immune disturbance. Id. at 529. They thought it conceivable that interleukin-13 is an important regulatory cytokine that both CD4+ and CD8+ cells produce from patients with nephrotic relapse. Id. at 536. Their laboratory was investigating the immunoregulatory actions of interleukin-13 on monocytes from patients with relapse of nephrotic syndrome. Id.

Petitioner filed as Exhibit 49 an article to which Dr. Quan referred in his supplemental expert report (Ex. # 40): Interleukin-13 expression before and after pulse treatment with methylprednisolone in children with steroid-responsive nephrotic syndrome, by H-K Jiang, et al., 9 CHIN J CONTEMP PEDIATR 6:533-36 (2007). Most of the article is in Mandarin, but the abstract is in English. The authors conclude from testing serum concentration and mRNA expression of interleukin-13 in children with steroid-responsive nephrotic syndrome that those levels increased, but methylprednisolone pulse therapy could inhibit the expression of protein and mRNA of interleukin-13 in those patients. Id. at 533.

Petitioner filed as Exhibit 50 an article to which Dr. Quan referred in his supplemental expert report (Ex. # 40): A Humanized Mouse Model of Idiopathic Nephrotic Syndrome Suggests a Pathogenic Role for Immature Cells, by A-L Sellier-Leclerc, et al., 18 J AM SOC NEPHROL 2732-39 (2007). After experiments with mice, the authors conclude that "it is tempting to propose that cells that are responsible for albuminuria are undifferentiated cells undergoing differentiation into T cells." Id. at 2736. They continue, "However, one cannot rule out the hypothesis that immature cells of other lineages may be responsible for albuminuria." Id.

Petitioner filed as Exhibit 51 an article to which Dr. Quan referred in his supplemental expert report (Ex. # 40): Epidemiology and Risk Factors for Thromboembolic Complications of Childhood Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) Study), by B.A. Kerlin, et al., 2009 J PEDIATR 1:105-10 (2009). The authors state that nephrotic syndrome is most commonly idiopathic and that thromboembolism occurs in 1.8% to 5% of children with idiopathic nephrotic syndrome. Id. at 105. The median age for diagnosis of nephrotic syndrome was 6.5 years of age. Id. at 106. The authors state that relapsing necrotic syndrome is common in childhood. Id. at 108. One of the most commonly identified risks of thrombosis is Factor V Leiden. Id. at 109.

Petitioner filed as Exhibit 52 a case report on two children to which Dr. Quan referred in

his supplemental expert report (Ex. # 40): Case Reports. Cerebrovascular Complications in Children with Nephrotic Syndrome, by M. Igarashi, et al., 4 PEDIATR NEUROL 6:362-65 (1988). The authors state arterial thrombosis is much less common than venous thrombosis and has been reported primarily in children. Id. at 365.

Petitioner filed as Exhibit 103 an article entitled Unraveling the immunopathogenesis of glomerular disease, by B.L. Dickinson, 169 CLIN IMMUNOL 89-97 (2016). Dickinson states the target of injury in glomerular disease is the filtration barrier, i.e., a structure composed of three parts: (1) a fenestrated endothelium, (2) the glomerular basement membrane ("GBM"), and (3) an epithelium comprised of unique epithelial cells called podocytes. Id. at 89-90. The endothelium is the first barrier and is permeable to cytokines, chemokines, antibodies, complement proteins, and other molecules. Id. at 90. The second layer, the GBM, prevents the passage of molecules, large anionic proteins, and cells into the subepithelial space. Id. The third layer is a single layer of podocytes, which are specialized polarized epithelial cells with slit diaphragms located between interdigitating foot processes. Id.

Dickinson then discusses innate immunity, stating that macrophages and neutrophils are the major effector cells of the innate immune system. Id. They detect pathogens and stimulate the release of proteases and reactive oxygen species to clear an infection, but which also causes collateral damage to tissues such as the glomerulus. Id. She notes that while macrophages are present in most tissues and function as sentinels throughout the body where the sites are vulnerable to infection, i.e., the skin and mucosal tissues of the respiratory, gastrointestinal, and urogenital tracts, macrophages are excluded from the glomerulus in the steady state. Id. Neutrophils are not normally found in healthy tissues but where there is inflammation, they capture, engulf, and kill pathogens and then die by apoptosis. Id. In contrast to the rapid response of the innate immune system, the adaptive immune response is much slower, evolving over five to seven days. Id. at 91. T and B lymphocytes and their soluble mediators make up the adaptive immune system. Id. Dickinson notes that early antibodies produced within weeks of exposure to an antigen during a primary immune response have a lower affinity for antigen than antibodies produced a month later, which exhibit a one-hundred fold increase in affinity. Id. at 93. She states that dendritic cells are innate immune cells and constitute the major antigen-presenting cells of the immune system. Dendritic cells also play a role in glomerular disease. She states glomerular disease is most often viewed as a manifestation of autoimmunity, the development of which depends on dendritic cells activation of autoreactive T cells with subsequent activation of autoreactive B lymphocytes. Id. In discussing alternatives to corticosteroids for treating glomerular disease, she mentions monoclonal antibodies, such as rituximab, which is specific for the B cell antigen CD20 and Belimumab, among other monoclonal antibodies. Id. at 95. She opines that dendritic-cell-based vaccines may one day be used to treat or prevent glomerular disease. Id.

Petitioner filed as Exhibit 104 an article entitled Childhood nephrotic syndrome--current and future therapies, by L.A. Greenbaum, et al., 8 NAT REV NEPHROL 445-58 (2012). (Respondent also filed this article as Ex. C, Tab 17.) The authors state that although edema and proteinuria were clinical symptoms for more than 2,000 years, only in 1484 has nephrotic

syndrome been described and only named as such in 1929. Id. at 445. Before glucocorticoids or antibiotics were available, 67 percent of children with nephrotic syndrome died. The mortality rate dropped in 1939 with the advent of sulfonamides.[27] The mortality rate dropped to 35 percent in 1944 following the use of penicillin. In the 1950s, the mortality rate fell to nine percent after the introduction of adrenocorticotropic hormone ("ACTH")[28] and cortisone, which caused a marked reduction in proteinuria in many patients. Id.

The authors state, "Although glucocorticoids have continued as the mainstay of therapy for nephrotic syndrome for more than 50 years, neither the target cell nor the mechanism of action of these agents in nephrotic syndrome has been clearly determined. Furthermore, although the majority of treatments found to be effective in treating nephrotic syndrome have been immunosuppressive, a minority have been thought to act by nonimmune mechanisms, and a few actually through immunostimulation." Id. The authors state that nephrotic syndrome is "clearly not a single disease." Id. They divide children with nephrotic syndrome into two groups: (1) corticosteroid-resistant, and (2) corticosteroid-sensitive, but note that the specific medications used for both groups are virtually identical. Id. They note that over the past decade (i.e., between 2002 and 2012), extensive research "has highlighted the crucial importance of the podocyte as a site of cellular injury in nephrotic syndrome." Id. The authors review drugs that have been traditionally used, but then switch to newer drugs, such as rituximab.[29] Id. at 447. They note that reports of rituximab inducing remission of nephrotic syndrome "have led to a re-evaluation of the inter-relationship between nephrotic syndrome and the immune system." Id. at 448. They continue:

> Although most historical evidence has suggested involvement of T cells, the effectiveness of rituximab in nephrotic syndrome implies a potential role of B cells in the development of nephrotic syndrome. However, the novel finding in 2011 that rituximab binds directly to an acid sphingomyelinase-like phosphodiesterase 3b (SMPDL3B) on the surface of podocytes suggests an even more direct mechanism of action for this drug in nephrotic syndrome.

Id. The authors mention the successful use of galactose[30] in treating nephrotic syndrome in its

[27] A sulfonamides is "an organic compound containing the –SO2NH2 group . . .; any of a class of drugs, the sulfa drugs, which are derivatives of sulfanilamide, competitively inhibiting folic acid synthesis in microorganisms and formerly bacteriostatic against gram-positive cocci (streptococci and pneumococci), gram-negative cocci (meningococci and gonococci), gram-negative bacilli (*Escherichia coli* and shigellae), a wide variety of other bacteria, and some protozoa. Because many strains of bacteria have developed resistance to sulfonamides, particularly to agents used singly, they have largely been supplanted by more effect and less toxic antibiotics, and when used are generally combined with another sulfonamide or other antimicrobial agent." Dorland's at 1802.

[28] ACTH acts like corticotropin, "a 39-amino-acid anterior pituitary hormone, one of the derivatives of pro-opiomelanocortin; it acts primarily on the adrenal cortex, stimulating its growth and the secretion of corticosteroids." Dorland's at 422.

[29] Rituximab is "a chimeric murine/human monoclonal antibody that binds the CD 20 antigen; used as an antineoplastic in the treatment of CD20-positive, B-cell non-Hodgkin lymphoma . . . ." Dorland's at 1650.

[30] Galactose is "an aldohexose epimeric with glucose at the 4 carbon but less soluble and less sweet, occurring naturally in both D- and L- forms (the latter in plants); it is a component of lactose and other oligosaccharides,

ability to alter glomerular permeability and decrease this permeability activity after IV administration to patients. Id. at 449. They mention testing of adalimumab, a monoclonal anti-tumor necrosis factor antibody, which has been associated with both remission and induction of nephrotic syndrome. Id.

The authors discuss the use of thiazolidinediones, a drug approved to treat type 2 diabetes mellitus, a therapeutic in nephrotic syndrome because it has beneficial effects on the kidneys. Id. at 450. Thiazolidinediones reduce proteinuria, microalbuminuria, podocyte injury, vascular injury, inflammation, and fibrosis in both diabetic and non-diabetic nephropathy. The success of the treatment is thought to be through direct renal protective effects, partially because of the direct action of thiazolidinediones on podocytes. Id. Among the known molecular effects of thiazolidinediones is their ability to decrease the glomerular production of transforming growth factor ("TGF")-ß, which is a key mediator of renal injury. Id. The authors state, "Of potential relevance to nephrotic syndrome, cultured podocytes treated with thiazolidinediones mimicked some podocyte responses to glucocorticoids, or had additive effects with them." Id. The authors suggest that use of thiazolidinediones to treat nephrotic syndrome "might enable a reduction in glucocorticoid exposure or improvement in their efficacy." Id. at 451. They conclude:

> In summary, thiazolidinediones slow the progression of glomerular diseases, and have also been shown to directly protect podocytes. Such findings suggest that thiazolidinediones might, therefore, have considerable potential as a therapy for nephrotic syndrome, even though the mechanisms of action are only partially understood.

Id.

The authors note the increased p38 MAPK activation in biopsied podocytes from adults with various forms of nephrotic syndrome. Id. Cell injury in podocytes involves both p38 MAPK and MK2. Id. Protein kinase C alpha ("PKCα") loss has podocyte-protective effects in mice. Id. PKCα seems to be a regulator of podocyte survival and proteinuria and might play an important role in several glomerular diseases. Id. at 452. Inhibiting PKCα is a potential strategy to protect podocytes in glomerular disease. Inhibiting PKCα, p38MAPK, and MK2 (all of which affect the same signaling pathway at different levels) seems "an exciting potential strategy to treat nephrotic syndrome in both children and adults" to the authors. Id.

The authors move on to Notch signaling which affects among other things a loss of mature podocyte characteristics. "Indeed, the severity of glomerular injury has been suggested to depend on Notch-regulated balance between podocyte death and regeneration provided by progenitor cells." Id. They state Notch signaling seems to play a key role during nephrogenesis but is mostly silent afterwards. Reactivation of Notch signaling in podocytes is associated with renal injury. They see an opportunity to treat nephrotic syndrome by inhibiting the Notch pathway in mature podoctyes, thus treating the podocyte injury associated with nephrotic

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cerebrosides and gangliosides, and various glycolipids and glycoproteins." Dorland's at 754.

syndrome. One method is use of γ-secretase-mediated cleavage of the Notch receptor. Id.

The authors discuss inhibiting cytokines, although "no single cytokine has been shown to have a direct causative role in nephrotic syndrome. . . ." Id. at 453. Interleukin ("IL")-13 can be a target for inhibition as a potential effective therapy. An IL-13 antibody (lebrikizumab) is effective to treat asthma and might be effective in nephrotic syndrome. Id. The authors move on to a discussion of a cellular stress response called stress-induced disturbance of protein folding in the endoplasmic reticulum, called the unfolded protein response ("UPR") which they say has a pathogenic role in some forms of nephrotic syndrome. Id. They then focus on oxidative stress, which is involved with nephrotic syndrome and other kidney diseases. Id. at 454. Developing improved or targeted strategies to reduce podocyte oxidative stress would be appropriate to attenuate podocyte injury in nephrotic syndrome. They note dietary supplementation with the antioxidants probucol[31] and Vitamin E in children with nephrotic syndrome has provided modest evidence supporting this approach. Id. The authors conclude:

> For more than 50 years, glucocorticoids have been the mainstay of therapy for children with nephrotic syndrome. Despite this, neither their target cell nor the mechanism of action in nephrotic syndrome is clearly known. . . . [Because of the partial effectiveness of these drugs and their marked adverse effects,] new therapies to treat nephrotic syndrome are urgently required. Several currently available drugs developed for other purposes are now being employed in the treatment of nephrotic syndrome, and have the potential to become standard therapies in the future. In addition, the recognition of the crucial role of podocyte injury in nephrotic syndrome has led to many new studies that have identified several important molecular pathways that are able to regulate podocyte injury. Development of drugs able to regulate these pathways offers hope for the availability of targeted and effective treatments for nephrotic syndrome in the future.

Id.

Petitioner filed as Exhibit 105 a case report entitled Membranous Nephropathy and Severe Acute Kidney Injury Following Influenza Vaccination by C. Patel and H.H. Shah, 26 SAUDI J KIDNEY DIS TRANSPL 6:1289-93 (2015). A 60-year-old woman received the 2009 H_1N_1 flu vaccine and two weeks later went to the emergency room with fever, intermittent nausea and vomiting, and lower extremity edema. Id. at 1290. She said that onset was "soon after being immunized." Id. She had seen her PCP one day before her ER visit because of worsening bilateral lower extremity edema. She was given furosemide and metolazone for edema, amlodipine and clonidine for hypertension, and prednisone for her membranous nephropathy and acute kidney injury. Id. at 1291. She achieved complete remission after one relapse. Id. at

[31] Probucol is "an anticholesteremic, used especially as an adjunct to diet for the reduction of elevated serum cholesterol in primary cholesterolemia. . . ." Dorland's at 1516.

1292. The authors thought that the woman's abrupt onset of nephrotic syndrome suggested the flu vaccine activated her immune system. It was unclear to the authors why their patient relapsed. She responded well to the second round of corticosteroids. Id. They suggest further studies to investigate the exact pathogenesis of flu vaccine-induced membraneous nephropathy. Id. at 1293.

Petitioner filed as Exhibit 106 a case report entitled Can influenza H1N1 vaccination lead to the membranous glomerulonephritis?, by A. Kutlucan et al., 55 INDIAN J PATHOL MICROBIOL 2:239-41 (2012). The authors describe the case of a 56-year-old man who received monovalent influenza A (H_1N_1) vaccine and developed a flu-like illness diagnosed as membranous glomerulonephritis ("MGN") **23 days after vaccination**. Id. at 239. The patient was put on prednisolone, acetylsalicylic acid, atorvastatin, and lysinopryl. Treatment lasted three months and ended. Id. The authors note that studies show the immunogenic response to H_1N_1 vaccine develops on the 23rd day after vaccination. Id. at 240. The authors found significant that the "emergence of the [MGN] illness and development of [the] immunogenic effect of the [H_1N_1] vaccine" on the 23rd day post-vaccination was **simultaneous**. Id. The authors state the precise reason for the MGN and renal involvement following H_1N_1 vaccination was unclear, but thought it possible that a disposition to autoimmune renal disease might cause MGN. Id.

Petitioner filed as Exhibit 107 a case report: Serious Adverse Reactions Associated with Over-the-counter Drugs, 293 PHARMACEUTICALS & MED DEVICES 16-17 (August 2012).[32] A boy under the age of 10 received flu HA (hemagglutinin) vaccine. The prior year, when he received flu HA vaccine, he developed fever and swelling at the vaccination site. When he received the current flu HA vaccine, eight hours after vaccination, his left axilla (armpit) swelled and the vaccine site also swelled down to the elbow. He had swollen lymph nodes in the left axilla and swelling on the left upper arm (vaccine site). One day after vaccination, he had fever in the 38 degree range Celsius (100.4 degrees Fahrenheit). His left axilla swelling was less. Id. at 16. Three days later vaccination, he had generalized swelling again and his weight increased. Id. at 16-17. He also had an increase in his urine protein. Id. at 17. He was diagnosed with nephrotic syndrome from which he recovered 21 days after vaccination. Id.

Exhibit C, Tabs 1-8, consist of the articles to which Dr. Kaplan referred in his expert report (Ex. C). Exhibit C, Tab 1, is an article entitled Predicting First-Year Relapses in Children With Nephrotic Syndrome, by A.R. Constantinescu, et al., 105 PEDIATRICS 3:492-95 (2000). The authors intended to find what could predict the chance of relapse in children with idiopathic nephrotic syndrome. Id. at 492. They found the earliest predictor of a relapsing course could be the number of days it took the patient to enter remission after treating with prednisone. Id. at 494. Patients who took longer to respond tended to have frequent relapses or were steroid-dependent. Id. A majority of patients will respond within the first three weeks after beginning steroid therapy. Id.

Exhibit C, Tab 6, is a case report entitled Close association between proteinuria and

[32] NEPHROTIC SYNDROME, www.pmdma.go.jp/english/safety/info-services/drugs/medical-safety-information/0001.html (last visited April 12, 2018).

regulatory T cells in patients with idiopathic nephrotic syndrome, by T. Kimata, et al., 28 PEDIATR NEPHROL 667-69 (2013). The authors discuss whether or not circulating regulatory T cells ("Tregs") are increased or decreased when a child with idiopathic nephrotic syndrome is exposed to a viral infection. The answer depended on the type of viral infection. Measles infection suppresses T cells. Id. at 667. But the five-year-old child who was the subject of the case report had influenza B virus which increased his regulatory T cells. Id. at 667, 669. Thus, the authors considered the influenza B virus infection to have caused the child to have a remission of nephrotic syndrome. Id. at 669. Previous reported exacerbations of nephrotic syndrome were associated with influenza A virus, including pandemic H_1N_1 viral infection. Id.

Exhibit C, Tab 7, is an article entitled Association of influenza vaccination with reduced risk of venous thromboembolism, by T. Zhu, et al., 102 THROMB HAEMOST 1259-64 (2009). The authors discovered that flu vaccine can reduce the risk of venous thromboembolism. Id. at 1261. They thought flu vaccination might lower the risk of thrombosis in some unknown ways other than by preventing flu infection. Id. at 1262.

An article to which Dr. Kaplan refers in his supplemental expert report (Ex. G) is Measles in the Nephrotic Syndrome, by A.H. Rosenblum, et al., 35 J PEDIATR 5:574-84 (1949). The authors state, "The clinical picture of the nephrotic syndrome is studded with remissions and exacerbations." Id. Of seven cases of nephrotic syndrome in which the children contracted wild measles virus, three showed marked and lasting improvement, three showed transient improvement, and one showed no response. Id. at 584. The authors state that "in some cases of the nephrotic syndrome a remission follows infection with measles." Id.

Attached to Dr. Bellanti's supplementary report (Ex. # 28) is a page (also marked as Ex. #28) from the IOM's ADVERSE EVENTS ASSOCIATED WITH CHILDHOOD VACCINES: EVIDENCE BEARING ON CAUSALITY 28 (K.R. Stratton, et al., eds., National Academy Press 1994), including the following under the heading "Biologic Plausibility:"

> All of the vaccine-adverse event associations assessed in this report have some biologic plausibility, at least on theoretical grounds. That is, a knowledgeable person could postulate a feasible mechanism by which the vaccine could cause the adverse event. Actual *demonstration* of biologic plausibility, however, was based on the known effects of the natural disease against which the vaccine is given and the results of animal experiments and in vitro studies. Only demonstrated biologic plausibility was considered by the committee in reaching its causality judgments. [emphasis in original].

Attached to Dr. Bellanti's supplementary report (Ex. # 28) as Exhibit 35 is a case report entitled Fulminant Cerebral Infarctions With Membranous Nephropathy, by S. Chaturvedi, 24 STROKE 3:473-75 (1993). The author states that nephrotic syndrome has been associated with both venous and arterial thromboses. Id. at 473. He describes the case of a 37-year-old woman

who died from fulminant multifocal thromboses and whose autopsy showed left hemispheric and right cerebellar infarction plus membranous nephropathy. Id. She had membranous glomerulonephritis. Id. at 474. The author comments that "the reported cases of cerebral infarction and nephrotic syndrome have lacked a unifying hematologic factor." Id. at 475.

Attached to Dr. Bellanti's supplementary report (Ex. # 28) as Exhibit 36 (and also filed as Exhibit 39) is a case report entitled Cerebral Infarction in Patients With Nephrotic Syndrome, by E.E. Marsh, et al., 22 STROKE 1:90-92 (1991). The authors describe two cases involving men with nephrotic syndrome who had cerebral arterial strokes. Id. at 90. The authors attribute their isolated cerebral arterial infarcts to a hypercoagulable state related to nephrotic syndrome. Id. at 92. They state the mechanism by which nephrotic syndrome causes a hypercoagulable state is unclear. Id.

Attached to Dr. Bellanti's supplementary report (Ex. # 28) as Exhibit 37 is a case report entitled Cerebral Infarction as a Complication of Nephrotic Syndrome: A Case Report with a Review of the Literature, by Y.W. Yun, et al., 19 J KOREAN MED SCI 2:315-19 (2004). The authors focus on a 53-year-old man who had cerebral arterial infarction associated with focal segmental glomerulosclerosis. Id. at 316.

Affidavits

On June 10, 2012, petitioner signed an affidavit. Ex. 5. Petitioner is a "trained immunization pharmacist." Id. at 1. He notes that J.M.'s urine is monitored daily each morning using Multistix to test for proteins in his urine, which would indicate a relapse of his nephrotic syndrome. Id. The day after J.M. received flu vaccine on October 1, 2009, his urine protein levels were markedly higher. Id. at 2.

Calendars

Exhibit 15 consists of three months, August – October 2009, in which J.M.'s blood pressure, whether he had protein in his urine, and weight are recorded. In the months of August and September 2009, J.M. did not have any protein in his urine as none is noted. Id. at 1, 2. On September 30, 2009, J.M. weighed 119 pounds. Id. at 2. On October 1, 2009, J.M. weighed 124 pounds, for a gain of five pounds in one day. Id. On October 2, 2009, the morning after vaccination that occurred the afternoon of October 1, 2009, petitioner measured J.M.'s protein in the morning (Ex. 17, at 1 [petitioner's timeline]). J.M. had +3 in the Multistix testing for protein in his urine. Med. recs. Ex. 15, at 3. Since the interval between the late afternoon vaccination and the next morning when petitioner measured J.M.'s urine for protein is approximately 16 hours, J.M.'s rise in protein occurred within less than one day of flu vaccination. By October 29, 2009, J.M. weighed 147 pounds or 28 pounds more than he weighed on September 30, 2009. Id. He had a reading of +2 in the Multistix testing for protein in his urine on October 31, 2009. Id.

VAERS Report

On January 17, 2012, petitioner completed a Vaccine Adverse Event Reporting System ("VAERS") form, stating that J.M. received flu vaccine at 2:30 p.m. on October 1, 2009 and had an adverse event at 7:30 a.m. on October 2, 2009 when elevated protein levels in his urine were detected. Ex. 16, at 1.

TESTIMONY

On October 17, 2017, the first day of the two-day hearing, petitioner testified first. Tr. at 4. Petitioner is a pharmacist. Id. He described J.M. as a well child with rare illnesses. Id. at 5. In 2007, J.M. developed nephrotic syndrome for which he took enalapril[33] but switched to prednisone. Id. In addition, he took Norvasc or one of the other ACE inhibitors.[34] Id. J.M. went into remission and had zero proteinuria in the beginning of February 2008. Id. at 6.

Petitioner kept track of J.M.'s proteinuria with a dipstick with a Multistix. Id. He and his wife checked J.M.'s proteinuria daily until four years before trial. Id. J.M. was negative on the dipsticks from February 2008 until June 2009. Id. Early in 2009, the family had been on a vacation and J.M. had a little bump in urine protein. Id. Through a phone consultation with the nephrologist Dr. Seikaly's office and through his nurse practitioner, they decided J.M. might have a relapse. Id. at 7. The proteinuria went to zero within two weeks. After that, Dr. Seikaly decided to use a prolonged protocol and J.M. used prednisone for an additional two months or two and one-half months. Id.

They saw Dr. Seikaly in August 2009 and he felt the taper of prednisone was working. Id. They spoke on August 14, 2009, and Dr. Seikaly mentioned J.M. receiving vaccination because of the 2009 pandemic. Id. at 8. Dr. Seikaly wanted J.M. to receive both the trivalent flu vaccine and the H_1N_1 monovalent vaccine. Id. The day after Thursday, October 1, 2009, the dipstick showed that proteins had climbed. Id. at 9. By the following Monday, J.M.'s protein was more of an issue as was his puffiness. Id. Petitioner brought J.M. in to see the doctor and the staff did not find any viruses, bacteria, or infections that could have triggered it. Id. at 9-10. The staff told him they suspected it was probably related to the vaccine, but they thought it would probably go away. Id. at 10. They started J.M. on another round of prednisone about a week afterwards. J.M. was on prednisone for about two months, but every time he tapered to 10 mg or between 10 and 20 mg, he had another relapse and the proteinuria returned. Id.

J.M. did not go into full remission until well after the strokes, i.e., sometime in 2013 or 2014. Id. at 11. J.M. went off steroid treatment when Dr. Quan tapered him down and in May 2010, Dr. Quan had a biopsy done. From the biopsy, Dr. Quan diagnosed J.M. with minimal change nephrotic syndrome. Dr. Quan switched J.M. to tacrolimus, whose brand name is Prograf. Id. Prograf is not a steroid, but lowers the immune response. Id. at 12. In late June 2011, Dr. Quan started to taper Prograf and J.M. started to have a bump in his proteinuria. The family was on vacation in Dallas and J.M. had a stroke in the hotel room. Id. at 12. In the

[33] Enalapril is "an angiotensin-converting enzyme inhibitor with antihypertensive and vasodilator actions." Dorland's at 611.

[34] ACE inhibitors are "angiotensin-conserving enzyme" inhibitors. Dorland's at 940.

hospital, J.M. had two more strokes. Id.

On cross-examination, petitioner stated that after J.M. received flu vaccine on November 19, 2008 when he had been in remission for over nine months, he did not have a bump up in his protein. Id. at 15-16. Before J.M. was diagnosed with nephrotic syndrome in late August or early September 2007, petitioner noticed J.M. had a general swelling which seemed a little odd. Id. at 16. Dr. Frank did a full checkup on J.M. and thought he was having some kind of allergic generalized reaction. Id. at 17. He prescribed antihistamines. Two days later, on a Sunday, J.M.'s parents took him to several different emergency rooms where personnel eventually figured out that J.M. probably had nephrotic syndrome and sent him to Children's Hospital where he was admitted on September 6, 2007. Id.

Initially, J.M. was on prednisone for five months, from September 6, 2007 to January 28, 2008. Id. at 18. J.M. was also placed on hypertensives on which he stayed even when he stopped taking prednisone in January 2008. Id. at 19. After J.M.'s first relapse of nephrotic syndrome in June 2009, he was on prednisone from June 15 to September 13, 2009, about three months. Id. at 23. In June 2009, J.M. had a little puffiness in his first relapse. Id. He called Dr. Seikaly and told him that J.M. had swelling in his face and abdomen. Id. at 24. He also had weight gain and an increase in blood pressure. Id. J.M. is no longer on antihypertensives or renal medication. Id. at 24-25.

When petitioner measured J.M.'s protein, weight, and blood pressure, it was always in the mornings between 7:30 a.m. and 7:45 a.m. Id. at 25-26. That was the weekday routine, but on weekends, it might be a little bit later. Id. at 26. His wife would keep track of the information as she printed out the calendars. Id. He would do the readings and give that information to his wife who put it on the calendar. Id. at 27. A lot of times, he would enter the information because she was at work. Id. The information on the calendar was created contemporaneously. Id. For protein testing, he used Multistix. Id.

J.M.'s last day on prednisone before the October 1, 2009 flu vaccination was September 13, 2009. Id. at 28. J.M.'s weight from September 13 through September 30, 2009 was stable in the 119- to 120-pound range. Id. J.M. received flu vaccine at 3:30 to 4:00 p.m. after school on October 1, 2009. Id. at 29. On October 1, 2009, J.M.'s weight was 124 pounds. Id. J.M.'s weight increased five pounds between September 30th and October 1st. Id. Petitioner agreed. Id. It was a fairly rapid onset. Id. The five-pound weight gain occurred before vaccination since petitioner recorded J.M.'s weight around 7:30 or 7:45 a.m. Id. at 30.

Petitioner then made various statements to explain away the significance of J.M.'s having gained five pounds from the day before (September 30, 2009) and that his five-pound gain occurred before he received flu vaccine in the afternoon of October 1, 2009. Petitioner first said scales can be plus or minus five pounds or so. Id. He then said he could not say whether he weighed J.M. in the morning on that day. Id. at 31. He said, "It's too far back." Id. He said he did not necessarily do any weighing in the morning. He said he sometimes weighed J.M. in the evening. Id. He said J.M. could have been wearing different clothes that day. Id. at 31-32.

Petitioner added, "And like I said a 5-pound weight gain is not really that big of a difference." Id. at 32. When respondent's counsel informed petitioner that a five-pound weight gain for a person J.M.'s size was a five percent increase in weight, petitioner said, "No. If I – if he's wearing shoes and everything. I don't recall exactly how he [sic] measured that. If that – if that's the basis of the whole thing, then I don't know – I don't know." Id. Petitioner said he did not know if J.M. weighed himself on October 1, 2009. Id. at 33. J.M. would get on the scale and tell petitioner what the number was. Id. at 34. Petitioner said he did not know if J.M. were wearing shoes on that day. Id. at 33. He said, "I can tell you right now, I can lose five, 10 pounds with taking off my clothes." Id. Petitioner finally said that the five-pound weight gain could be inaccurate. Id. at 35.

The undersigned asked petitioner at that point if it would not be important to have consistency in weighing J.M. Id. at 36. Petitioner responded, "[W]ell, no. Because we're not doing clinical data." Id. The undersigned asked petitioner why he and his wife were weighing J.M. Id. at 37. He responded, "[I]f there's a drastic change in the weight, then there's definitely something the doctors would want to do . . . ." Id. The undersigned asked petitioner what "drastic" meant to him and he replied, "A rapid change or a quick change." Id. at 38. The undersigned asked how much of a change and petitioner said a ten-pound weight gain. Id. Petitioner admitted he had no recollection of a prior five-pound weight gain in J.M. either before August 2009 or after October 2009. Id. at 38-39.

By October 29, 2009, J.M.'s weight had reached 147 pounds. Id. at 33. In other words, he had gone from 119 pounds on September 30, 2009, to 124 pounds on October 1, 2009, to 147 pounds on October 29th for a total of a 28-pound weight gain in one month.

Respondent's counsel asked petitioner if J.M. had any fever or local reaction to the flu vaccine he received in the late afternoon of October 1, 2009. Id. at 40-41. Petitioner said there was "nothing really outstanding or noticeable, but that very well could have happened. . . . I don't think [J.M.] had anything that was significantly noticed but it's possible there was." Id. at 41.

On redirect, petitioner went back into explaining why a five-pound weight gain was meaningless:

> And, again, part of – part of the weight has to do with clothing and such, and, you know, kids wear big shoes some days and they don't wear big shoes other days. It just kind of – kind of varies on basis of the scale's accuracy as well as other things.

Id. at 51. Petitioner also testified that both Dr. Seikaly and his nurse practitioner Becky told him that the likely trigger of J.M.'s nephrotic syndrome relapse was the flu vaccination. Id. at 52.

Dr. Albert Quan, J.M.'s treating pediatric nephrologist, testified next. Id. at 53. He has been practicing nephrology since 1989. He was a faculty member at the University of Texas

Southwestern Medical Center from 1993 to 2005. Id. Since January 2006, he has been a clinical nephrologist at a local hospital in Dallas. Id. at 53-54. He has been J.M.'s treating nephrologist since the middle of 2010. Id. at 54.

Dr. Quan defined nephrotic syndrome as "a group of disorders whereby the kidney leaks out a lot of protein from the body, the blood primarily, into the urine." Id. This results in low protein in the body, leading to a lot of edema, swelling all over the body, and high cholesterol and high lipid levels. In children, one particular condition is known to cause the majority of nephrotic syndrome disorders. It is called minimal change disease or minimal change nephrotic syndrome. Id. It is easily treatable with steroids or prednisone. Id.

Dr. Quan said that after J.M.'s initial course, starting in September 2007, he had a slightly longer period of steroids than most people. Id. at 55. But J.M. did respond to the steroids and was in remission until over a year later when he had his first relapse in June 2009. Id. Dr. Quan said many patients with nephrotic syndrome have relapses. Id. Typically, a relapse follows some kind of viral illness, a cold or flu or something of that nature. Id. at 56. He said many (he also said most) children relapse within six months of onset. Id. He considered J.M. lucky to have not have a relapse until over a year and one-half after onset. Id.

Dr. Quan testified there was nothing unusual about J.M.'s first relapse in June 2009. Dr. Seikaly put him on prednisone again, which is the usual treatment. Id. He went into remission on June 23, 2009, 13 days after restarting steroids, which Dr. Quan said is very typical, i.e., to go into remission within a couple of weeks of restarting steroids. Id. at 56-57. Then, Dr. Seikaly weaned J.M. off steroids and, by late August or early September 2009, he was off them. Id. at 57. Dr. Quan deemed J.M. an infrequent relapser of nephrotic syndrome, and patients like that typically have a very good prognosis. Id.

Dr. Quan said that after J.M. relapsed in October 2009, his nephrotic syndrome changed from what it had been before. Id. After the second relapse, when Dr. Seikaly attempted to wean J.M. off steroids, J.M. relapsed again, whereas before October 2009, he was able to wean J.M. off steroids. Id. In December 2009, when J.M. was tapering steroids, he had a relapse in January 2010. Id. at 57-58. Dr. Quan considered all of J.M.'s subsequent relapses just a sustained relapse rather than a new relapse. Id. at 58. When J.M. became Dr. Quan's patient, he put him on Prograf which got him under good control, and he was able to be weaned off steroids for about a year. Id. at 58-59. Dr. Quan had J.M. on Prograf until June 2011. Id. at 59. A couple of months later, in August 2011, J.M. had a relapse, and Dr. Quan put him back on steroids. Shortly thereafter, he had a stroke and two other strokes. Dr. Quan put J.M. back on prednisone and Prograf. Id. In nephrotic syndrome, someone can lose certain proteins that favor clotting in the blood and Dr. Quan believes that is what happened to J.M. Id. The incidence of strokes in children with nephrotic syndrome is not very common. Id. at 60. It is more common in adult forms of nephrotic syndrome which are caused by different diseases, usually with membranous nephropathy which occurs with certain types of cancers. Id. at 61. J.M. had a relatively atypical course. Id.

Dr. Quan said a prolonged relapse that the doctor cannot get under control means J.M. was continuing to lose protein in his urine which would tip the balance toward clotting in his blood. Id. When J.M. got off Prograf in June 2011, Dr. Quan thought he was going to do well and not have any further relapses. Id. at 62. Unfortunately, by August 2011, he relapsed which at that point was related to his stroke. Id. Most nephrotic syndrome patients get some kind of illness, a viral illness, typically a cold or flu, before they relapse. Id. at 62-63. Presumably, he said, the immune system is upregulated at that point and, then, somehow, makes the kidney membrane more permeable so that the patient loses protein in the urine leading to nephrotic syndrome. Id. at 63. It makes sense, Dr. Quan said, that if someone's immune system is upregulated through immunization, a similar effect can also occur. This has been reported in the medical literature. Id. Any vaccine could do that. Id.

Dr. Quan thought that temporally and plausibly, more likely than not, "flu vaccine led to J.M.'s new onset of his latest relapse that finally led to his stroke." Id. at 64. A poorly controlled nephrotic syndrome has a higher risk of stroke or any other type of clotting complication. Id. Most of the time, doctors can control a relapse of nephrotic syndrome. Id. Prior to October 1, 2009, J.M. had had only the onset of nephrotic syndrome and one relapse a year and one-half later. Id. at 64-65. He would have considered J.M. to be under good control with just steroids and to have a good prognosis. Id. at 65.

When petitioner's counsel asked Dr. Quan what the effect of the flu vaccination would have been on J.M. if he started relapsing before he received the flu vaccine on October 1, 2009, Dr. Quan said:

> That would be impossible to say exactly. I think I would venture to say that, if he was ready to relapse again, that the flu shot might make that worse. But, again, there's no evidence that that's going to be the case.

Id. at 66. Practitioners generally do not immunize patients who are in the middle of tapering steroids on a relapse during the time they are tapering. Id. at 67. They wait until the tapering is done and the patient has cleared from the relapse. Dr. Quan thinks that most nephrologists think that an immunization can be a risk factor in causing a relapse. Id.

Dr. Quan testified that J.M. has not had any more relapses since the one that led to his stroke in 2011. Id. at 67-68. Dr. Quan saw J.M. two or three months before the hearing and he continued to do well without any nephrotic syndrome relapses at all. Id. at 68. The strokes however have left sequelae. Id. Dr. Quan said there was nothing in his medical records other than the flu vaccination that can be identified as causing the change from few relapses and steroid sensitive to steroid dependent and long-term immunosuppression with steroids and Prograf. Id.

On cross-examination, respondent's counsel asked Dr. Quan if he had written any publications on nephrotic syndrome in general. Id. at 69. Dr. Quan said he had not. In addition,

he has not written on minimal change nephrotic syndrome specifically.

The first time Dr. Quan saw J.M. was May 13, 2010. Id. at 70. Dr. Quan agrees that weight gain is a sign or symptom of a relapse of nephrotic syndrome. Id. at 74-75. He reiterated his prior testimony that, if the relapse occurred before vaccination, there is no evidence of which he is aware that vaccination would have made the relapse worse. Id. at 75. He repeated, "There's no way to prove that the flu vaccine made anything worse or not." Id. at 76. The undersigned then asked Dr. Quan if the flu vaccination altered J.M.'s course if his relapse began before the vaccination. He replied, "I don't – I don't know that I can answer that accurately. . . . So the effect of the flu vaccine exactly on his relapse at that point, I can't say with – with complete honesty. I don't know." Id. at 78.

Respondent's counsel asked Dr. Quan if he considers a five-pound one-day weight gain in a 119-pound boy to be a significant weight gain. Id. at 79. Dr. Quan said yes. Dr. Quan continued Dr. Seikaly's practice of putting J.M. on hypertensives even when he was in remission. Id. at 80. He did this because he was concerned about J.M.'s blood pressure levels. Id. When Dr. Quan weaned J.M. off Prograf in June 2011, he wanted J.M. to catch up with all his immunizations. Id. at 85. Dr. Quan knows that J.M. has a factor V Leiden mutation which is associated with an increased risk of blood clots. Id. When J.M. had his strokes in August 2011, Dr. Quan reinitiated his prednisone and Prograf. Id. at 86. Dr. Quan weaned him off Prograf in March 2013 and off prednisone in 2012. Id. at 86-87.

Dr. Quan stated that pieces of data, such as using immune suppressants to treat any relapses occurring after viral illnesses, strongly suggest that the immune system may play an important role in nephrotic syndrome. Id. at 91. Dr. Quan agreed that the onset of J.M.'s proteinuria was less than 24 hours after flu vaccination, much shorter than the onset of nephrotic relapse or syndrome in the case reports filed with his reports. Id. at 94. The morning after his late afternoon flu vaccination, J.M. had a protein count in his urine of plus 3. Id. at 96. Although Dr. Quan put the onset of J.M.'s relapse in his January 2, 2015 report (Ex. # 40) as four to five days, he agrees that it actually occurred within 24 hours of vaccination. Id. at 97. Most of the onsets of relapses in the case reports to which Dr. Quan referred in his reports occurred longer than within a day after vaccination. Id. at 100.

At this point, on redirect, petitioner's counsel showed a Japanese government document warning that flu vaccine can cause nephrotic syndrome, a document not admitted into evidence that Dr. Quan, respondent's counsel, respondent's experts, and the undersigned had never seen. Id. at 103. Respondent's counsel objected because the time period for submitting exhibits in the case had long passed. Id. at 103-04. Respondent's counsel also objected to six new medical articles referenced in Dr. Bellanti's forthcoming PowerPoint presentation, none of which was part of the record. Id. at 104. The undersigned did not permit petitioner's counsel to ask Dr. Quan questions about a document he had never seen, but did permit petitioner's counsel to save the document for Dr. Bellanti. Id. at 105.

On redirect, Dr. Quan said that normally weight gain and elevation in protein go hand in

hand because the loss of protein in urine leads to onset of edema and weight gain. Id. at 107. He does not think that the weight gain occurring earlier or a day later changes the fact that before the vaccination, J.M. was a well-controlled patient, infrequently relapsing, and then after the vaccination, he became a frequent relapser. Id. at 108. That J.M. has a factor V Leiden mutation does not affect his opinion that one of the complications of nephrotic syndrome is abnormal clotting. Id. at 109. The factor V Leiden could have added some additional risk, but it was not the only risk factor for J.M.'s clotting problem. Id.

As for any vaccination being an immune stimulator causing a nephrotic syndrome relapse, one would need to see this happen more often. Id. He thinks the immune stimulation is more important than the identity of the vaccine. Id. at 110.

On recross, Dr. Quan said that he would not consider the five-pound weight gain before the flu vaccination on October 1, 2009 to be indicative of a relapse in J.M.'s nephrotic syndrome when the protein in his urine on the same day was negative. Id. at 112, 113. Dr. Quan said he looks at the trend, not a one-day measurement of weight. Id. at 115. Dr. Quan agreed that the trend starting the morning of October 1, 2009 was his weight started to increase up to 147 pounds on October 29, 2009. Id. Dr. Quan agreed that J.M. had a trend of weight gain starting before he received flu vaccine, saying, "That's what it would seem to be; right." Id. at 115-16.

Dr. Joseph A. Bellanti, petitioner's expert immunologist, testified next. Id. at 118. He is a professor of pediatrics and microbiology immunology emeritus and director of the International Center for Interdisciplinary Studies of Immunology at Georgetown University Medical Center. Id. at 119. He has held many national presidencies of national organizations: the Society for Pediatric Research, the American College of Allergy & Immunology, the American Association of Medical Laboratory Immunologist, and Interasma. Id. at 120. He has published over 400 scientific articles in peer-reviewed journals, including many books. His most recent textbook of immunology is Immunology IV, Clinical Applications in Health and Disease, published in 2012. Id.

Dr. Bellanti testified that there is little dispute that the 2009 flu vaccination was causally related to the development of J.M.'s unfortunate downhill medical course. Id. at 122, 123. J.M.'s infrequent relapse rate pre-vaccination and excellent response to steroids indicated to his nephrologist that J.M.'s subsequent course would be uncomplicated with few relapses, if any. Id. at 124.

Dr. Bellanti reviewed J.M.'s flu vaccinations. Id. The first flu vaccine he received was the live attenuated intranasal flu vaccine (FluMist) on November 20, 2006. On November 19, 2008, he received his first inactivated flu vaccine. On October 1, 2009, he received his second inactivated flu vaccine. Id. This last vaccination led to his relapse on October 2, 2009. Id. at 125. Following this flu vaccination, J.M. developed steroid-dependent or steroid-resistant nephrotic syndrome. Id.

Dr. Bellanti began an explication of the immune system, stating it is everywhere and

constantly looking for foreignness. Id. at 128. The immune system has three functions: defense, homeostasis, and surveillance. Id. Dr. Bellanti said he was not calling J.M.'s disease an autoimmune disease, but "there are components of the immune system that are directed against renal tissue. So in a sense, you might consider it an autoimmune expression of the immune system." Id.

Dr. Bellanti then divided his discussion of the immune system into three parts: (1) the innate system, (2) the adaptive system, and (3) the immune system and disease. Id. at 129. The innate system consists of many inflammatory cells, mediator cells, and complement natural killer cells. If foreignness can be removed at that point, the immune system does not have any further role. Id. But most of what people encounter involves the adaptive system which involves the T-cell and B-cell systems. Id. at 130. The B-cell system in its differentiated form makes five classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. Id. The T-cell system has many daughter cells which have different functions: Th1, Th17, Th2, T-reg cells. Those T cells can be divided into two universes, the Th0 cells which is the helper population, the CD4+, and the CD8s, the killer cells that kill virally-infected cells and tumors. Id.

Dr. Bellanti said the immune response responds to an action and to a reaction. Id. at 131. Cytokines are molecules that cause the cells of the immune system to talk to one another. Id. at 132. Foreignness produces proinflammatory cytokines. Id. at 131-32. Some cytokines promote inflammation, while others neutralize inflammation (the anti-inflammatory cytokines). When the proinflammatory and anti-inflammatory cytokines are in balance, the individual is healthy. Id. at 132. Vaccinations can cause a disequilibrium when there are too many proinflammatory cytokines produced and not enough anti-inflammatory cytokines to counterbalance. Id.

People are born with the innate system. Id. The innate system consists of phagocytic cells which include macrophages, polymorphonuclear leukocytes, eosinophils, and dendritic cells. Id. at 133. A group of cells are called mediator cells, which are mast cells and basophils. Id. These cells get fired off with atopic or allergic disease by procuring mediators such as histamine and globulins and others, the natural killer cells which help fight cancer and viral infection complement, involved in neutralizing bacteria, combining with antibodies, making complexes, and putting holes in cells with bactericidal activity. Id. at 134. There are also innate T cells. Id.

Dr. Bellanti said that injury occurs not only from adaptive immunity, but also from innate immunity. Id. Innate immunity responses occur within minutes, hours, or days. Adaptive immunity takes a few weeks to be stimulated. Id. Dr. Bellanti said, "So as we'll see in the case of J.M., there is evidence that innate immune injury may be playing a role in the pathogenesis of his condition." Id.

Dr. Bellanti described the adaptive system as consisting of T cells (Th1, Th17, Th2, Th3, Tr1) and B cells which interact with each other. Id. at 135. The Th2 cell interacts with the B cell to make gamma globulins. IgG is made of four subclasses. At birth, the baby receives the transfer of IgG from the mother which falls rapidly during the first months of life. Then the baby

make his or her own gamma globulins. Id. IgM appears first. Id. Then IgG, IgE, and IgA appear later. Id. at 136.

By the time J.M. developed nephrotic syndrome in 2007, he was six years old and his gamma globulins, that is, his immune system, were fairly well developed but not completely. Id. Gell & Coombs developed the four mechanisms of immunologic injury in 1963. Type I is where IgE binds to a mast cell and, when coupled with antigen, releases mediators. Id. Type II is the cytotoxic reaction when antibody can kill a cell, usually in the presence of a complement.[35] Id. at 136-37. Type III is when immune complexes composed of antigen-antibody and complement produce inflammation and serum sickness-like immune complex inflammatory disease. Id. at 137. Type IV is when the T cell damages by way of its subsets. Id. Dr. Bellanti said this classification suffers because it is based entirely on components of the adaptive immune system, without taking into consideration injury by the innate system. Id. Dr. Bellanti said we need a new system. He suggests a new system in chapter 17 of his book because many diseases we are now recognizing do not fit within the response of the classic Gell & Coombs adaptive system. We need to look at the innate system. Id. The innate system has immediacy of action so that when foreign configuration hits these cells, mediators are rapidly released, some of which have been described in the pathogenesis of the nephrotic syndrome. Id. at 141.

Dr. Bellanti stated:

> Nephrotic syndrome does not fit nicely into the Gell & Coombs. It's not a Type I IgE. It's not – at least we're not sure it doesn't – the cytotoxic IgG is Type II. Immune complexes may be involved in certain forms of the nephrotic syndrome, but the type we're talking about with J.M., the idiopathic or the minimal change disease, MCD, has been a mystery since I was a resident in Buffalo. You know, we were wondering what is this nephrotic syndrome. It sometimes occurs after a stinging bee or a Dilantin drug or an infection. It didn't fit neatly into this Gell & Coombs, and that's the point that I wish to make.

Id. at 141-42.

The undersigned responded to Dr. Bellanti:

> SPECIAL MASTER MILLMAN: Well, I -- when I was reviewing for this hearing, I vaguely recall that the concept even of what is the pathogenesis or the pathological manifestation of nephrotic syndrome is changing as we speak.

[35] Complement "is now used to refer to the entire functionally related system comprising at least 20 distinct serum proteins, their cellular receptors, and related regulatory proteins that is the effector not only of immune cytolysis but also of other biologic functions including anaphylaxis, phagocytosis, opsonization, and hemolysis." Dorland's at 393.

> THE WITNESS: As we speak.
> . . .
> SPECIAL MASTER MILLMAN: [T]hat concept of what underlies nephrotic syndrome is not that it's immune mediated, that it's some kind of I don't know what to call it. What is it? Do you have a word for this? What is this word?
>
> THE WITNESS: It's a – a complex pathogenesis involving many mediator systems and toxic components that are released during infection, during challenge with a drug, with a bee sting. It doesn't necessarily have to be a vaccine. But vaccine is one of them.

Id. at 142-43.

Dr. Bellanti testified that J.M. had an immediate response occurring within the first 24 hours which persisted with all of his recurrences, either with challenge with viral infection or flu vaccine "or whatever." Id. at 153. J.M. had a continuum of damages which the innate immune system initiated but the adaptive system perpetuated. Id.

Dr. Bellanti said that the reason we call nephrotic syndrome a "syndrome" and not a "disease" is that a disease has a single etiology, but a syndrome has many etiologies. Id. at 153-54. Nephrotic syndrome refers to a group of kidney disorders involving loss of protein through the kidneys, called proteinuria, leading to low protein levels in the blood, predominantly called hypoalbuminemia, causing water to be drawn into soft tissues, called edema. Id. at 154.

The nephrotic syndrome that J.M. has does not have too many inflammatory cells. Id. at 155-56. J.M. has primary nephrotic syndrome, which means nephrotic syndrome in the absence of systemic disease. Id. at 157. The reason that Dr. Quan diagnosed J.M. with minimal change disease after J.M.'s biopsy in 2010 was that there was minimal inflammation. Id. at 158. Dr. Bellanti stated that flu vaccine promotes a tremendous outpouring of cytokines and other substances that can contribute to chronicity in rare cases. Id. at 159. Circulating factors could be involved after flu vaccination. Id. at 162-63. Antigen-antibody complexes could also be involved but they are less likely because they would cause more inflammatory involvement rather than a mixed minimal change disease. Id. at 163.

Dr. Bellanti stated that J.M. received three flu vaccines: the first, intranasal flu vaccine, on November 20, 2006; the second, inactivated flu vaccine on November 19, 2008; and the third, the "punitive vaccine," an inactivated flu vaccine on October 1, 2009, which led to the relapse of nephrotic syndrome beginning on October 2, 2009. Id. at 164. Dr. Bellanti attributes J.M.'s quick reaction to the 2009 flu vaccine to an anamnestic response since J.M. received two prior flu vaccines in 2006 and 2008. Id. at 165. The third flu vaccine in 2009 constituted a rechallenge. Id.

Dr. Bellanti said the normal immune response does not give someone kidney disease. Id.

at 166. Why is J.M.'s case different? Dr. Bellanti said probably genetics played a major role and doctors have not begun "to scratch the surface on that." Id. Dr. Bellanti agreed that J.M. did not have any systemic signs of a cytokine reaction to flu vaccination. Id. at 168. J.M. did not have fever or arthralgia. Id. Dr. Bellanti said that something happened to J.M. that was localized, not systemic. Id. at 169. "There's not a systemic cytokine storm as we sometimes see. It's a localized thing that's going on." Id. The damage was localized to J.M.'s kidneys. Id.

Dr. Bellanti said that, if J.M. were beginning a relapse before receiving flu vaccine on October 1, 2009, the flu vaccine would only increase his susceptibility. Id. at 189.

On cross-examination, Dr. Bellanti agreed that it is hard to predict which children will be steroid resistant and which will be steroid dependent. Id. at 219.

The undersigned asked Dr. Quan if there were a natural course of minimal change nephrotic syndrome. Id. at 224-25. Dr. Quan responded, "But you don't really know, nobody has a crystal ball to tell you exactly how well they're going to do. There are certain factors that increase or decrease the risk of certain things happening and that's the best you can do." Id. at 225. Dr. Quan also said that minimal change nephrotic syndrome is a different disease in adults than in children. Id. at 232. The underlying reason for the difference in adults compared to children is that there is a different cause of minimal change nephrotic syndrome in adults than the cause in children. Id.

Dr. Bellanti admitted on cross-examination that all of the studies to which he referred in his expert reports and testimony concerned nephrotic syndrome in adults except for one which dealt with children who had minimal change nephrotic syndrome and thrombosis, but were not vaccinees. Id. at 233, 234. He agreed that minimal change nephrotic syndrome in adults is different than in children. Id. at 233. None of the studies to which Dr. Bellanti referred in his expert reports and testimony concerning nephrotic syndrome had onset within 24 hours. Id. at 234.

Although Dr. Bellanti stated that flu vaccine led to J.M.'s relapse, causing more proteinuria and more hypercoagulability due to loss of urinary proteins, he also admitted that J.M. could spontaneously lose enough protein in his urine to achieve hypercoagulability. Id. at 242. It could occur independently from flu vaccination or flu vaccination could cause it. Id. In fact, other medications that J.M. took could play a role. Id.

On the second day of the hearing, counsel returned with information about the components of the 2008 and 2009 flu vaccinations J.M. received. J.M. also previously had an intranasal flu vaccination on November 20, 2006. Id. at 270. That vaccine plus the two inactivated flu vaccines (in 2008 and 2009) were all similar, containing two A viruses consisting of H_1N_1 and H_3N_2 plus a B virus. Id. Petitioner stated that J.M. never received flu vaccine before the intranasal flu vaccination on November 20, 2006. Id. at 276.

Since Dr. Bellanti's explanation for the quickness of J.M.'s 3+ proteinuria the morning of

October 2, 2009 was an anamnestic response due to his having received flu vaccine in 2008, the issue was whether the difference in the B virus component of the 2008 flu vaccine compared to the B virus component of the 2009 flu vaccine was an impediment to the theory Dr. Bellanti espoused in explanation of the quick interval between 3:30 or 4:00 p.m. on October 1, 2009 and the proteinuria the morning of October 2, 2009. Dr. Bellanti said J.M. had a hypersensitivity response. Id. at 267. In Dr. Bellanti's opinion, having two out of the three flu vaccine components in 2008 and 2009 identical was sufficient for J.M. to have an anamnestic response the day after his October 1, 2009 flu vaccination. Id. at 277. He thought a year between the two vaccinations was appropriate for an anamnestic response to happen in that length of time. Id. at 278. He said immunological memory lasts a long time. Id. at 279.

Dr. Bellanti also thought J.M.'s 2006 intranasal flu vaccination played a role in the quick interval between his 2009 flu vaccination and his proteinuria within a day of vaccination even though the 2006 intranasal flu vaccine did not have any components identical to the 2008 killed flu vaccine or the 2009 killed flu vaccine. Id. Dr. Bellanti explained that when he was at Walter Reed Army Institute of Research, Dr. Tommy Francis and other workers with flu vaccine spoke about "original immunologic sin" that was imprinted the first time someone was exposed to a virus. Id. at 279-80. In this view, every time someone is exposed to a new virus, there is some molecular mimicry or cross-reactivity to give that person an anamnestic response. Id. There is sharing of epitopes[36] so that whether the virus comes from Brisbane, Australia, Uruguay, or Florida, there is enough similarity with those antigenic epitopes to stimulate the anamnestic response. Id. In Dr. Bellanti's opinion, there was sufficient identity among the two A flu strains and one B flu strain to which J.M. was exposed in the intranasal vaccine of 2006, the killed virus vaccine in 2008, and the killed virus vaccine in 2009 to cause an anamnestic response in 2009 based on the prior two vaccines. Id. at 280.

The undersigned asked Dr. Bellanti why, after J.M. had the onset of nephrotic syndrome in September 2007 and went into remission in August 2008, he did not have a relapse when he received flu vaccine on November 19, 2008, since he already received flu vaccine on November 20, 2006. Id. at 285-86. Dr. Bellanti said "We obviously don't know the precise answer," but offered an opinion based on what we know about these vaccines. Id. at 286. Someone hopefully obtains protective immunity when he or she receives flu virus intranasally because the vaccine stimulates the IgA, not the IgG, and the secretions. Id. at 287. As it turns out, however, Dr. Bellanti noted, the Centers for Disease Control no longer recommends intranasal attenuated vaccine because it does not have the "punch" they hoped it would have. Id. Dr. Bellanti surmised that J.M.'s intranasal flu vaccine was alone not sufficient to give enough of an anamnestic response when he received his first inactivated flu vaccine in 2008. Id. The

[36] An epitope is an "antigenic determinant." Dorland's at 637. An antigenic determinant is "a site on the surface of an antigen molecule to which a single antibody molecule binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies of many different specificities." Id. at 502. An antigen is "any substance capable, under appropriate conditions, of inducing a specific immune response and with reacting with the products of that response, that is, with specific antibody or specifically sensitized T lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant … combines with antibody or a specific receptor on a lymphocyte." Id. at 103.

induction of memory cells J.M. obtained was largely from the 2008 flu vaccination. Id. at 289. J.M. was sensitized to the epitopes that are part of the killed virus in the flu vaccine. Id. Dr. Bellanti said unfortunately flu vaccine is only 50 to 70 percent effective, but it does give some benefit to blunting the disease. Id.

Dr. Bellanti recalled that Dr. Quan said that viruses, such as the common cold and other respiratory viruses, trigger many cases of nephrotic syndrome. Id. at 290. Too much of an immune response may trigger a relapse. Id. at 291. That could explain flu vaccine causing a relapse, but in the case of measles virus, you might see improvement. Id. With measles, someone gets anergy, i.e., too little response, but for the most part, infections heighten the immune response. Id. at 292.

Dr. Bernard Kaplan testified for respondent. Id. at 294. He is retired. Id. Before he retired in June 2016, he spent eight years at the Children's Hospital of Philadelphia. Id. at 295. His medical career started in Johannesburg, and proceeded to Montreal where he trained in pediatric nephrology. Id. at 296. He eventually came to the Children's Hospital of Philadelphia in 1987 where he was chief of nephrology. Id. at 297. He spent almost 30 years there. Id. Some 40 or 50 of his 400 articles are on glomerular disorders. Id. at 299.

Dr. Kaplan went to Montreal to work with Dr. Keith Drummond who had worked with Dr. Robert Good in Minnesota. Id. at 299. Dr. Good was a famous immunologist who opened up the field of immunopathology. Id. Dr. Drummond and Dr. Good with others showed immune deposits in post-streptococcal glomeruloneuritis and in Goodpasture syndrome. Id. But they were unable to show any immune pathology in minimal change nephrotic syndrome. Id. at 300. Because they were unable to show any evidence of immune pathology in minimal change nephrotic syndrome, the group in Minnesota and Dr. Drummond's lab started to study the biochemical structure of the basement membrane to try to understand whether there was an alteration in the biochemistry of the basement membrane. Id. Using rats, they administered puromycin or two anticancer agents, daunorubicin and Adriamycin, to see if there were structural change in isolated glomeruli. Id. There were biochemical changes. Id. In patients with infections such as congenital syphilis, thyroid disease, and candida infection, they saw syphilis bacterium and immune complexes in the kidney, thyroid antigen in the kidney, and candida antigen in the kidney. Id. at 300-01. But none of these patients had minimal change nephrotic syndrome. Id. at 301. Their disorders were completely different from minimal change nephrotic syndrome. The only aspect they had in common with minimal change nephrotic syndrome was a lot of protein in the urine. Id.

When Dr. Kaplan lived in Montreal, he saw children with minimal change nephrotic syndrome and wondered if mercury contamination due to the forestry industry near the St. Lawrence River were related to the children's nephrotic syndrome. Id. at 301-02. The link between mercury exposure and nephrotic syndrome had occurred in women who used mercury for cosmetic reasons in Africa, but Dr. Kaplan could not show an association in the Montreal children. Id. at 302. In Montreal, he worked with cancer patients who had nephrotic syndrome, but they were adults with a different form of nephrotic syndrome, i.e., the membranous form,

than children had. Id.

Dr. Kaplan mentioned that clots are extremely uncommon in people with nephrotic syndrome. Id. at 303. Prednisone does not cause renal venous thrombosis or any thrombi. Id. An imbalance between coagulant factors and anticoagulant factors can occur in nephrotic syndrome. Id. Clotting occurs more frequently in adults. Id. at 303-04. Children with nephrotic syndrome usually do not have proteinuria for a long time, which in theory explains why clots are relatively rare in children. Id. Adults with membranous nephrotic syndrome may have nephrotic syndrome for months or years because there still is not a good treatment for it. Thus they are more likely to get clots. Id. Both in the adult literature, and especially in the pediatric literature, one hardly ever sees arterial clots such as occurred in J.M. Id. at 304-05. In the pediatric literature, the ratio of venous to arterial clots is 20 to 1. Id. at 305. In adults, the ratio of venous to arterial clots is 3 to 1. There are other reasons why adults may have clots, such as arteriosclerosis, smoking, and obesity. Id.

Dr. Kaplan then said he became "profoundly interested" in the genetic basis of nephrotic syndrome because the hospital had a number of families where the mother and child had nephrotic syndrome or two children had nephrotic syndrome and they were minimal change nephrotic syndrome. Id. Other patients had focal sclerosis. By collaborating with people at Harvard, they were able to show in some of their patients with focal sclerosis that they had a mutation in a gene for podocin and for alpha-actinin 4. Id. Saying he had great respect for Dr. Bellanti, Dr. Kaplan identified a misstatement Dr. Bellanti made during the first day of testimony when he said the genetic causes of nephrotic syndrome occur in neonates and infants and not in older people. Id. at 305-06. This is a very old idea which has now been completely shown to be wrong. Id. at 306. There have been 20 mutations shown so far and they occur in older children and adults as well. Id. at 306. These mutations are in proteins that help to control the podocyte, which is an extraordinary cell that sits on the outer surface of the basement membrane and controls the basement membrane. Id.

Dr. Kaplan said that the podocyte has interdigitating processes that are like rafts of nephrin and podocin, which impede the passage of albumin. Id. at 306-07. If there is a disruption in the apparatus, albumin can pass through and nephrotic syndrome can occur. Id. at 307. In minimal change nephrotic syndrome, it is predominantly albumin that is lost since damage to the kidney is miniscule as light microscopy demonstrates. This compares with the membranous form of nephrotic syndrome and other forms in which immune complexes disrupt the architecture of the foot processes, causing massive leakage of all kinds of protein, not just albumin. Id. Dr. Kaplan has been involved in the care of hundreds of children with nephrotic syndrome, including many hundreds of children with minimal change or steroid-sensitive nephrotic syndrome. Id. at 310. He has also seen thousands of relapses. Id.

Dr. Kaplan's opinion is that the October 1, 2009 flu vaccine did not significantly aggravate J.M.'s minimal change nephrotic syndrome. Id. at 313. His opinion also is that the October 1, 2009 flu vaccine did not significantly aggravate J.M.'s minimal change nephrotic syndrome so as to cause his strokes 22 months later. Id. The percentages of different types of

nephrotic syndrome differ in children versus adults. Id. at 314. The majority of patients who were steroid sensitive had minimal change nephrotic syndrome. On the other hand, the majority of the patients who were steroid resistant had focal sclerosis. Id. Clinically, it is virtually impossible to differentiate between the two types of nephrotic syndrome. Id. Although a majority of patients with minimal change nephrotic syndrome responded to steroids usually within two to three weeks, some could not be weaned off steroids. Id. at 315. These children had breakthroughs where the parents checked for urine protein daily, but the reason for these patients' steroid dependence is not well understood. Id.

On the other hand, there are patients who go into remission on steroids, but a year or more years later, they become steroid resistant or steroid dependent. Id. Then, the doctor will add another medicine such as Prograf, but Prograf can damage the tubules of the kidney. Id. at 316. The patient could become dependent on Prograf. Id. Once weaned off Prograf, the patient may become steroid sensitive or remain in remission for a prolonged period of time. Id. at 317. That is why Dr. Kaplan believes that minimal change nephrotic syndrome behaves in a chaotic way. He had a patient who was in remission but, ten years later, the child had a relapse. Id.

Dr. Kaplan said that initially minimal change nephrotic syndrome was call Nil (as in "nothing") disease because if someone took a biopsy from a child with minimal change nephrotic syndrome and compared it to a biopsy from a child with normal kidneys, under the microscope someone would not see any difference. Id. at 319. They look absolutely the same on light microscopy. Id. You would not see an increase in the cells of the kidney that are active immunologically, such as T cells, B cells, and Th cells. Id. at 320. You would not see necrosis or death of any tissue or fibrin deposits. You would just see a normal glomerulus. Id. Dr. Drummond and his group stained the glomeruli for hemoglobin, IgG, IgA, IgM, and complement, and none of that was present in children with classic minimal change nephrotic syndrome. Id.

Biopsies examined under electron microscopes revealed effaced foot processes of the podocytes in the kidneys of children with minimal change nephrotic syndrome. Id. The term originally was "fused" because they looked as though they had become one cell or one component of the cell. Id. at 320-21. Studies have shown that this is a very dynamic process and reversible. Id. at 321. These foot processes were embedded in sialoprotein,[37] which is negatively charged. Sialoprotein coats platelets, red cells, and other cells preventing them from adhering or sticking to each other. Id. Albumin is also negatively charged. The impedance of the passage of albumin through the kidney involves not only the size of the foot process pores, but also the charge. Id.

Dr. Kaplan distinguished between the case reports petitioner filed dealing with nephrotic syndrome in adults allegedly due to flu vaccine. Id. at 324. In those cases, as one would expect in an adult population, they were mainly focal segmental glomerulosclerosis and membranous nephrotic syndrome. Id. at 324-25. J.M. does not have focal segmental glomerulosclerosis or membranous nephrotic syndrome. Id. at 325. The most common acquired cause of membranous

[37] Sialoprotein is "a glycoprotein that contains sialic acid as one of the carbohydrates." Dorland's at 1706.

nephrotic syndrome is hepatitis B virus. The antigen of the virus is demonstrated in the immune complexes, but this is not in minimal change nephrotic syndrome. Hepatitis C virus causes another kind of glomeruli disorder, but not minimal change nephrotic syndrome. Id.

Dr. Kaplan also distinguished between nephritis or nephritic syndrome, which manifests as blood and protein in the urine, and nephrotic syndrome, which manifests as predominantly albumin in the urine. Id. at 325-26. Nephritis is a term for inflammatory diseases, one of which is post-streptococcal glomerulonephritis in which leukocytes and other immunoreactive cells infiltrate the kidney, leaving immune deposits and causing blood in the urine. Id. at 326.

Dr. Kaplan said there is absolutely no evidence that minimal change nephrotic syndrome is an inflammatory disease. Id. at 327. The complement is not decreased. The immunoglobulin levels are actually decreased. There are no circulating immune complexes. Id. There are no infiltrates of cells into the glomerulus to make it an inflammatory condition. Id. at 327-28. There are no immune complexes in the kidney. Id. at 328.

Dr. Kaplan said he has not seen a different outcome in a child with minimal change nephrotic syndrome who gets sick with flu virus. Id. at 329. He also said he has not read anything that states that flu virus in any way changes the course or severity of nephrotic syndrome. Id. Most pediatric nephrologists have heard the idea that flu virus or any viral infection can trigger relapses of nephrotic syndrome. Id. As a pediatric nephrologist, he would recommend to mothers that they vaccinate their children and they would decline. Id. at 330. If the illness were not flu, but was chickenpox, measles, polio, or tetanus, the mothers would accept those immunizations. Id.

Dr. Kaplan said he does not think that flu vaccine in any way changed J.M.'s course. Id. But he said that, looking at his patients, he does not really know which of the children who had relapses of nephrotic syndrome had it because they did or did not receive flu vaccine. Id. What he does know is that in the entire medical literature, there is not a single case report of a child developing minimal change nephrotic syndrome following flu vaccination or relapsing following flu vaccination. Id. at 330-31. In the past 20 years, two or more than two billion flu vaccinations have been given in the United States alone, but the incidence of minimal change nephrotic syndrome has remained absolutely stable. Id. at 331.

The undersigned asked Dr. Kaplan if minimal change nephrotic syndrome was an immune-mediated disease. Id. at 332. Dr. Kaplan replied:

> [O]nce upon a time, people talked about [the] immunological basis of minimal change nephrotic syndrome as I myself did. But the world has changed. And it's changed very dramatically. And we have to take into consideration those changes that have occurred. And those changes relate to our whole new understanding of the biology of the podocytes what it – what its structure is, its sarcoskeleton, what maintains it, how it functions in terms of

> preventing proteinuria, and all the genes that are involved.
>
> And the fact that although people still say that Prednisone acts as an immunosuppressant in nephrotic syndrome or that Prograf acts as an immunosuppressant in nephrotic syndrome, firstly, there is absolutely no evidence for that whatsoever. And secondly, there is increasing evidence that Prednisone acts through angiopoietin 4 …, which is a chemical compound in the basement membrane, and that cyclosporine acts by stabilizing the podocytes, and that there are so many other receptors and – and proteins that are affected by different agents that people thought were immunologically mediated but more and more seem not to be immunologically mediated.

Id. at 334.

Dr. Kaplan and colleagues published a paper showing that treating a large number of children who had focal sclerosis (not minimal change) with prednisone and Prograf or with Vasotec (a blood pressure medication) made no different in outcome with the children who received Vasotec trending toward statistical significance. Id. at 334-35. Blood pressure drugs reduce protein in the urine and protect the kidneys. Id. at 334. This is an example "where all of our thinking changed from using very so-called immunosuppressive agents to using much less toxic agents." Id. at 335.

Dr. Kaplan agrees that J.M. had minimal change nephrotic syndrome starting in September 2007. Id. at 336. The glomeruli in minimal change nephrotic syndrome actually hyperfunction, i.e., work much harder than normal even though they are leaking protein, i.e., albumin. Id. at 337. The glomeruli normally filter the serum creatinine which the kidney excretes. The serum creatinine tends to be very low in children with minimal change nephrotic syndrome, maybe 0.1, 0.2, or 0.4. Id. But J.M., when he was initially hospitalized, had a serum creatinine of about 0.8 or 0.9 which became 1.6, which is quite high. J.M. had developed acute renal failure ("ARF"). The new term is acute renal injury. The causes of acute renal injury or failure are a decrease in blood volume, damage to the kidney, or a blockage to outflow of urine. Id. Dr. Kaplan said the reason for J.M.'s acute renal injury or failure was that he was "very volume-depleted" from vomiting, diarrhea, and loss of albumin in his urine. Id. It took J.M. a long time for his serum creatinine to come down to 0.8 or 0.9, but it did not come down to normal levels. Id. Dr. Kaplan said he would be very concerned about a patient with a first presentation of nephrotic syndrome whose creatinine was that high and it did not return to normal. Id. at 337-38. That would really worry him. Id. at 338.

That J.M.'s doctors prescribed first Norvasc and then atenolol soon after he presented with minimal change nephrotic syndrome tells Dr. Kaplan that they were really worried about J.M.'s blood pressure. Id. This was before he had been exposed to a long course of prednisone or gained a lot of weight. Dr. Kaplan said something was going on because, normally in minimal change nephrotic syndrome, blood pressure is not elevated. Id.

When respondent's counsel asked Dr. Kaplan if J.M. at the time of onset of his minimal change nephrotic syndrome or relapse had any type of trigger, Dr. Kaplan replied "at no time prior to onset or relapse did he ever have a high fever or any other features of … this acute innate response. He had nothing like that." Id. at 338-39. J.M. is similar to a large number of nephrotics who just present "out of the blue" without other symptoms. Id. at 339. J.M. continued to have proteinuria despite being on prednisone for a long time. Id. at 340. He was still spilling protein even though he was on 40 mg. of prednisone every other day. Dr. Seikaly, J.M.'s first nephrologist, expressed the concern that J.M. might relapse once prednisone was tapered. Id. Dr. Seikaly discussed with J.M.'s parents the use of tacrolimus and CellCept therapy and recommended CellCept if J.M. did not tolerate tapering of steroids. J.M. was tapered very slowly. Id. Dr. Kaplan said that "the idea of giving a five- or six-month course of Prednisone tells me as a pediatric nephrologist that this doctor [Dr. Seikaly] was having other sorts of thoughts because of the way that J.M. was behaving in his first episode [of minimal change nephrotic syndrome]." Id. at 340-41.

J.M.'s first relapse occurred in June 2009. Id. at 342. Between the onset of J.M.'s nephrotic syndrome in September 2007 and his first relapse in June 2009, J.M. had a flu vaccination on November 19, 2008, but he did not have any adverse reaction to it. Id. Turning to September 30, 2009, after J.M. had been weaned off prednisone, petitioner indicated that he would check J.M's urine each morning around 7:30 a.m. for protein, and measure his blood pressure and weight. Id. at 344. Dr. Kaplan found quite striking that on Wednesday, September 30, 2009, J.M. weighed 119 pounds, but the next day, on Thursday, October 1, 2009, he weighed 124 pounds. Id. at 344-45. There was no protein in his urine. Id. at 345. But on October 2, 2009, he had three plus protein in his urine. Id.

Dr. Kaplan said that from August 1, 2009 to September 30, 2009, J.M.'s weight was remarkably stable, fluctuating a little bit, but very stable. Id. at 345-46. But, on October 1, 2009, J.M. had a five-pound weight gain which equals more than two liters of fluid retention. Two liters of fluid retention is the cutoff used in adults below which you do not see edema. Above two liters, you start to see edema in adults. Id. J.M.'s weight does not go down on October 2, 2009. It is still 125 pounds the next day, increasing to 126 and 127 on successive days. "In other words, something changed on that particular day [October 1, 2009] that remains constant for the next few days." J.M.'s weight increases more as his proteinuria continues. "To a nephrologist, this can only mean one thing: that something has changed in his ability to excrete fluid," suggesting he had a relapse. Id.

In Dr. Kaplan's opinion, J.M. was already relapsing on October 1, 2009, "that he was one of these children who has an explosive relapse, a very rapid relapse." Id. at 347-48. By October 2, 2009, he already had protein in his urine with the same 125 pounds. Id. at 348. Dr. Kaplan said "that this change in his condition occurred prior to him getting the vaccine or even contemporaneously with getting the vaccine . . . ." Id. Dr. Kaplan does not accept that the five-pound weight gain was not the beginning of J.M.'s second relapse because his protein count was normal on October 1, 2009. The reason he does not accept that it was not the beginning of

J.M.'s second relapse is that J.M. had a sudden increase of two liters of fluid. Id. at 348-49. J.M.'s weight increase from 119 to 147 pounds from October 1-29, 2009 was significant to Dr. Kaplan. Id. at 349.

After the October 1, 2009 vaccination, but not because of the vaccination, J.M. had more difficulty in maintaining remission. Id. at 353. After his strokes, J.M.'s minimal change nephrotic syndrome went into remission and he has remained in remission and off all treatment. Id. at 354. Dr. Kaplan did not think that minimal change nephrotic syndrome is different in adults versus children, but that the dosage of medicine is incorrect in adults. Id. at 356-57.

Dr. Kaplan said Dr. Bellanti's description of the innate process and the adaptive mechanisms in the context of minimal change nephrotic syndrome, which Dr. Kaplan has been taking care of for 50 years, is not accurate. Id. at 362. Dr. Bellanti's schema and speculations are a theory in response to one of Dr. Kaplan's criticisms. Id. at 363. There is no evidence of any of this happening in children with minimal change nephrotic syndrome. Id. at 363. Dr. Kaplan disagrees with the Dickinson article which describes nephrotic syndrome as characterized by damage to podocytes driven by immune complexes in the subepithelial space. Id. at 364. Dr. Kaplan stated "there is absolutely no evidence for the presence of the immune complexes in the subepithelial space or anywhere else in the kidney in minimal change nephrotic syndrome." Id. Franklin's paper does not address minimal change disease, but a totally different syndrome from which she cannot extrapolate to minimal change disease. Id.

Dr. Kaplan discussed the Zhu paper, "Association of Influenza Vaccination with the Reduced Risk of Venous Thromboembolism" for the point that in the general population, flu vaccine significantly protected the recipients from developing a clot. Id. at 366. The suggestions that J.M.'s flu vaccination on October 1, 2009 caused a stroke 22 months later is "absolutely inconceivable." Id. The undersigned explained petitioner's theory that were it not for the flu vaccination on October 1, 2009, J.M. would not have relapsed and failed to respond to prednisone, been put on Prograf and, because of that, had strokes. Dr. Kaplan replied:

> So that's very Aristotelian, as Dr. Bellanti was trying to tell us about A to B to C. And life isn't Aristotelian. Certainly biology isn't. Biology is a shower of arrows. There is no direct Path A for anything anymore. Well, maybe there are some. But look at any diagram and what you see are arrows in every direction doing all kinds of things.
>
> And I think, with the greatest respect, to say that because he had the vaccine and relapse and then had another relapse and then had a stroke, that that was the cause – caused by the vaccine, I think that's inconceivable. That's not based on anything that – that can be somehow made into a coherent scientific story. It just doesn't make sense. Medically, it doesn't make sense.

Id. at 367-68.

The undersigned asked Dr. Kaplan why it did not make sense medically. Id. at 368. He replied that, first, it was a very long period after he received the vaccine. Secondly, he responded to treatment and went into remission. He subsequently relapsed, but we do not know if he would have relapsed anyway had he not received the vaccine. Dr. Kaplan suspects J.M. would have relapsed anyway. Then he had another relapse. Then, J.M. had an arterial thrombus. It bothers Dr. Kaplan "tremendously" why a young boy would have an arterial thrombus. Id. The idea was that it must be related to his nephrotic syndrome because of loss of factors in his urine. But it is extremely rare to see this in nephrotic syndrome in a child. Id. The arterial thrombus and specifically in the cerebral artery after J.M. had been in relapse for a very short time is puzzling because he did not really have a chance to lose massive amounts of procoagulation and anticoagulation factors that people talk about in those who have venous thrombi. Id. at 368-69. The mutation J.M. has in factor V Leiden does not cause bleeding, contrary to what Dr. Bellanti said. Id. at 369. It causes clotting. Id. Dr. Kaplan cannot ascribe J.M.'s strokes to the flu vaccine or to his nephrotic syndrome. Id. at 370. He has never seen a single case of a cerebral artery thrombus in a child with nephrotic syndrome. Id.

Dr. Kaplan then discussed the Greenbaum paper. Id. at 373. A coauthor Dr. Smoyer trained under Dr. Kaplan, and Dr. Kaplan knows Dr. Greenbaum well. Greenbaum and his two-coauthors as well as the authors of several other important papers express doubt that there is an immunopathogenesis or cytokine pathogenesis for minimal change nephrotic syndrome. Id. at 374. This change in understanding the nature of minimal change nephrotic syndrome arose because of the "amazing discovery of the mutation of the nephron in congenital nephrotic syndrome which just totally changed the whole view of nephrotic syndrome." Id. at 375. The change has been so significant that a new term has been created to describe all these conditions: podocytopathies.

Dr. Kaplan disagrees with Dr. Quan's view that after October 1, 2009, J.M. never went into remission, i.e., that his second relapse continued for years. Id. at 390-91. Dr. Kaplan said that J.M. did not have a completely smooth course after October 1, 2009 because he had relapses. Id. at 391. However, J.M. sustained a prolonged remission of 11 months while on Prograf. Id. at 391-92. In June 2011, J.M.'s parents asked Dr. Quan to stop the Prograf. Id. at 392. J.M. had another relapse by the end of July 2011. The nephrotic syndrome did not respond to prednisone, he had the cerebral vascular accidents, and then he responded to prednisone. Id. J.M. had six relapses: June 2009 (before the flu vaccination at issue); October 1, 2009 (the date of vaccination); December 2009 (when prednisone was being weaned); March 2010 (when prednisone was being tapered); May 9, 2010; and June 2011 (when taken off Prograf). Id. at 392-93. Most nephrotic syndrome is treated with steroids. Id. at 393. Steroids are anti-inflammatory. It is more problematical whether they have effects on the immune system per se. They are related to the immune system and can suppress it. Id.

The undersigned asked Dr. Kaplan the following:

SPECIAL MASTER MILLMAN: If minimal change nephrotic

> syndrome is a podocytopathy and not an immune-mediated illness, why, then, would a drug like Prednisone affect the course of the disease since that is anti-inflammatory?
>
> THE WITNESS: Well, this – this question had no clear answer for the longest time. We were using Prednisone without having the faintest idea what it was – what its pathways were, what it was doing in terms of minimal change nephrotic syndrome, until this paper that appeared two years ago which I've referred to [as] Clements paper [Ex. 16, Tab 16]. It appeared in Nature, and they suggested that the steroids were having an effect on the podocytes and the basement membrane through this Angiopoietin 4 chemical which has nothing to do with the immunological factors.
>
> And – and so this is still an evolving subject where people are now trying to understand how these agents are working by focusing on the cell that's injured in this condition, i.e., the podocytes rather than looking at other cells in the body.

Id. at 395.

Dr. Kaplan mentioned Dr. Glassock who was one of the preeminent nephrologists in the world who spent a career studying nephrotic syndrome. Id. at 397. Dr. Kaplan said that Dr. Glassock shifted completely away from the immune pathogenesis of nephrotic syndrome to the theories about which Dr. Kaplan was speaking (Ex. C, Tab 14). Dr. Kaplan also mentioned Dr. William Couser who was also a world expert on nephrotic syndrome and he does not mention minimal change nephrotic syndrome as an immune-mediated condition in his paper Dr. Kaplan submitted (Ex. 0) which reviews the whole subject of nephrotic syndrome. Id.

Dr. Arnold Levinson, an immunologist, testified next for respondent. Id. at 400. Before he retired, he had been the University of Pennsylvania School of Medicine chair of the Penn Center for Clinical Immunology, chair of the Allergy and Immunology Department and its training program director. Id. at 403-04. He has taught clinical immunology, which was translating basic immunology into clinical medicine, particularly related to hypersensitivity disorders, including autoimmune diseases, immune deficiency, and allergic diseases, to medical students, residents, and fellows. Id. at 404. He has conducted research on autoimmunity and published papers on hypersensitivity responses to drug treatment. Id. at 406. He has also served as a reviewer on peer-reviewed journals such as the Journal of Allergy and Clinical Immunology, Clinical Immunology, the Journal of Neurologic Science, the Journal of Clinical Investigation, Lancet, and others. Id. He was elected president of the Clinical Immunology Society, and chair of the American Board of Allergy and Immunology, which certifies people in allergy and immunology. Id. at 407.

Dr. Levinson's opinion is that the October 1, 2009 flu vaccination did not lead to a relapse of J.M.'s nephrotic syndrome or exacerbate a relapse. Id. at 409. He also opined that the

October 1, 2009 flu vaccination did not lead to J.M.'s CVA. Id. at 410. Dr. Levinson does not agree with petitioner's hypothesis using the innate immune system and adaptive immune system in this case. Id. at 111. Dr. Bellanti's testimony is that there is an innate immune component that accounts for the rather brisk development of proteinuria following the October 1, 2009 flu vaccination. Id. at 412. Dr. Bellanti's second point is that an adaptive immune response occurred days to weeks later for the chronicity or the relapses of J.M.'s illness post-vaccination. Id.

Dr. Levinson said that when immunologists discuss an anamnestic response, they are talking about a specific immune response which occurs after a patient encounters an antigen which the patient had encountered before. Id. at 413. When immunologists discuss specific immune responses in an adaptive immune response, they are talking about T-cell responses and B-cell responses that are antigen specific. Id. A quickened response occurs anywhere from three to seven days later. Id. at 414. In minimal change nephrotic syndrome, there is no inflammatory reaction. Id. at 415. Dr. Levinson said there is no evidence of any immunologic reactants detected within the involved kidney. We are not dealing with a specific antigen-induced T-cell response or antibody response that anyone knows about in minimal change nephrotic syndrome. Id. We are not dealing with membranous nephropathy where there is an autoantibody that reacts with a podocyte antigen called PLA2R.[38] Id. In minimal change nephrotic syndrome, it does not matter if the flu vaccine J.M. received in 2009 shared some of the same components that were in the flu vaccine J.M. received in 2008. Id. at 416. Antigen-specific T cells are not involved in the pathogenesis of minimal change nephrotic syndrome. Dr. Bellanti's presentation is irrelevant to this case. Id.

Dr. Levinson said that petitioner has a problem explaining in immunologic terms J.M.'s proteinuria within 24 hours of his October 1, 2009 vaccination. Id. at 418. The needle with the flu vaccine was not injected into J.M.'s kidney but into a remote muscle, probably the deltoid. Id. Petitioner has to explain how the vaccine injected into the deltoid ends up not only in the kidney, but in the epithelial podocytes, a very special compartment of the kidney. Id. Dr. Bellanti's explanation was the vaccine induced a tremendous cytokine response, but he has no evidence for that. Id. at 419.

Dr. Levinson also took issue with conceiving of the innate immune response as having a memory so that exposure to a prior flu vaccine would cause a faster response. Id. at 422. There is no memory in an innate immune response. It does not need to see an antigen or foreign substance more than once to respond. Its response will not increase if it has previously seen a cell before. Id. Therefore, when J.M. received flu vaccine in 2008, why did he not make an innate immune response to that flu vaccine? Id. at 423. Why did he supposedly make it to the 2009 flu vaccine since repeated exposure does not affect the innate immune response? Id. Antibodies are not secreted for a period of a few days to several days. Id. at 429.

J.M. did not have any fever after his October 1, 2009 flu vaccination. Id. at 432. He did not have any myalgia or local vaccine site reaction. Id. at 433. When a lot of cytokines are

[38] PLA2R is phospholipase-A2-receptor. See generally Dorland's at 1438.

involved, they manifest clinically by myalgias, muscle aches, arthralgias, joint aches, fevers, and headaches. Id. If J.M. had been developing a strong innate immune response to the point of altering the function of epithelial podocytes, he should have had some of these symptoms. Id. In addition, because the vaccine is injected into muscle, he should have had a local reaction to the injection because of the innate immune response, but J.M. did not. Id. at 433-34. Nothing in J.M.'s records or the testimony indicates that he ever had local or systemic reactions to any of the vaccines he received in his life, including the October 1, 2009 flu vaccination. Id. at 434.

In explaining how steroids treat minimal change nephrotic syndrome, Dr. Levinson said steroids have minor immunosuppressive activity and major anti-inflammatory activity. Id. at 436. Minimal change nephrotic syndrome has undergone a major metamorphosis in terms of our understanding of it from what used to be thought to be predominantly an immune-mediated disease to a whole new understanding from the molecular biological understanding of podocytes and podocyte function. Id. at 437. Thus, because medical thinking used to be that minimal change nephrotic syndrome was immune-mediated, steroids were used to treat it. It turns out, however, that steroids have direct effects to protect podocyte function. Id. at 436-37.

The undersigned asked Dr. Levinson the following:

> SPECIAL MASTER MILLMAN: [W]hat I think you're saying is that because the concept of what minimal change nephrotic syndrome has changed from thinking it to be an inflammatory disease, maybe immune mediated, and then recognizing it's neither, and yet when they use steroids Prednisone, Prograf, which are anti-inflammatory, or they use multiple immune modulators all ending in "mab," that these work and they shouldn't work, but they do work that there's a … something they don't know that's also happening in these drugs which benefit[s] the podocytes that are affected by minimal change nephrotic syndrome.
>
> Am I summing up what you said?
>
> THE WITNESS: That's fine.

Id. at 439.

The undersigned asked Dr. Levinson if he would say that because nephrologists continue to treat children who have minimal change nephrotic syndrome with prednisone or Prograf or with immune-modulating drugs that are not steroids, this proves minimal change nephrotic syndrome is an inflammatory or immune-mediated disease. Id. at 441. Dr. Levinson replied he would absolutely not say that. Id.

Petitioner put Dr. Bellanti on rebuttal. Id. at 459. Dr. Bellanti said in ancient times medicine started with belief and faith. Id. at 461-62. As time passed, medicine moved from belief and faith to magic and imagination. Id. at 462. Dr. Bellanti quoted Einstein as saying that

imagination is probably more important than knowledge.[39] Id. Dr. Bellanti asked who is going to quibble with Einstein. Id. He continued that, ultimately, medicine is based on research, knowledge, and science. He thinks Dr. Kaplan's and Dr. Levinson's testimony is based less on science and facts but more on belief and imagination. Id. He said Dr. Kaplan "hobbles around the belief [a]nd doesn't really get into the science." Id. Dr. Bellanti said the medical literature strongly supports a role of infection, particularly viral infection, in the relapse of nephrotic syndrome. Id. at 462-63. Dr. Bellanti disagreed with Dr. Levinson's testimony, stating "he skirted around the issue [of the innate immune system]." Id. at 465.

Dr. Bellanti agreed with Dr. Kaplan and Dr. Levinson that the T-cell theory once popular in medical literature concerning nephrotic syndrome has been pretty demolished. Id. on 468. Dr. Bellanti believes that the spectrum of cytokines released in J.M.'s early response explains J.M.'s relapse on October 1, 2009 when he received the vaccine and had a one-day relapse with proteinuria and the continuation of that process. Id. Dr. Bellanti admitted that J.M. did not have cytokine responses (fever, aches) to the flu vaccine administered October 1, 2009 but insisted cytokines from the innate system are responsible for some of the symptoms following flu vaccine. Id. at 469. The following colloquy occurred:

> SPECIAL MASTER MILLMAN: But he didn't have any of those symptoms. You're saying that his alleged relapse is a symptom. He didn't have soreness in his arm. He didn't have swelling in his arm. He didn't have fever. He didn't have arthralgia. He didn't have myalgia. All he had was a relapse of his minimal change nephrotic syndrome. You're calling that a symptom of cytokine effect due to the vaccine.
>
> THE WITNESS: When they do occur, but I'm saying that there could still be these factors that were in the belief, imagine – imagination, and these permeability factors, I think many of those are cytokines.
>
> SPECIAL MASTER MILLMAN: I'm not going into magic or imagination or belief or faith because I have my marching orders [from] the [F]ederal [C]ircuit. [I]t requires that I find – and I haven't ruled, obviously, but that I find a reasonable, [plausible], scientific or medical theory explaining how flu vaccine can cause a relapse of minimal change nephrotic syndrome. Well, we don't get [that] yet. . . .[N]one of it deals with belief, faith, magic, or imagination. So you can get rid of four of those six [boxes of nouns (faith, belief, magic, imagination, research, knowledge) Dr.

[39] The actual quotation is "I am enough of the artist to draw freely upon my imagination. Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world." Jeff Nilsson, Albert Einstein: "Imagination Is More Important Than Knowledge", THE SATURDAY EVENING POST (March 20, 2010), http://www.saturdayeveningpost.com/2010/3/20/history/post-perspective/imagination-important-knowledge.html.

Bellanti put up for display about which he discussed].

Id.at 469-71.

Dr. Bellanti then agreed that the Greenbaum article, published in 2012, refuted and dismissed the old T-cell theory of minimal change nephrotic syndrome. Id. at 473-74. Dr. Bellanti still felt that some of "these belief, faith factors" may be based on data related to factors coming from the innate immune system. Id. at 474.

DISCUSSION

To satisfy his 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. Sec'y of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of Health and Human Services, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

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

418 F.3d at 1278.

Without more, "evidence showing an absence of other causes does not meet petitioner's affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. Id. at 1148.

Petitioner must show not only that but for flu vaccine, J.M. would not have had the second relapse of his minimal change nephrotic syndrome, but also that flu vaccine was a substantial factor in causing J.M.'s second relapse of his minimal change nephrotic syndrome. Shyface v. Sec'y of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

Moreover, petitioner alleged that flu vaccine significantly aggravated J.M.'s minimal change nephrotic syndrome by causing a relapse which then resulted in a much more serious form of minimal change nephrotic syndrome ending in three strokes. The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." Section 300aa-33(4). No expert doubted that J.M.'s course was significantly worse after his October 1, 2009 flu vaccination. The issue is whether or not the vaccine was a substantial factor in significantly worsening his minimal change nephrotic syndrome. There is also a subsidiary issue whether J.M.'s five-pound increase in weight on October 1, 2009 occurred before he

received flu vaccine and manifested the first symptom of his relapse before his vaccination.

The Federal Circuit in W.C. v. Sec'y of HHS, 704 F.3d 1352, 1357 (Fed. Cir. 2013) adopted the test in Loving v. Sec'y of HHS, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009), as "the correct framework for evaluating off-table significant aggravation claims." The Loving test has six parts:

> (1) the person's condition prior to administration of the vaccine,
> (2) the person's current condition (or the condition following the vaccination if that is also pertinent),
> (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to the vaccination,
> (4) a medical theory causally connecting such a significantly worsened condition to the vaccination,
> (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and
> (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Id. at 144.

Two preliminary issues present in this case: (1) is minimal change nephrotic syndrome an immune-mediated illness as the medical profession once believed or is it a podoctyopathy as the medical profession currently believes; and (2) do prior flu vaccinations create an anamnestic response so that a flu vaccination can cause a relapse of minimal change nephrotic syndrome within one day without any systemic symptoms such as fever, malaise, lethargy, arthralgia, etc.

Two patriarchs of medicine testified in this case: petitioner's expert Dr. Bellanti, a patriarch of immunology, and respondent's expert Dr. Kaplan, a partriarch of pediatric nephrology. Both are giants in their respective fields. In addition, J.M.'s second treating pediatric nephrologist, Dr. Quan, testified for petitioner, and Dr. Levinson, an immunologist with his own distinguished career, testified for respondent.

From Dr. Kaplan's testimony, the undersigned learned that minimal change nephrotic syndrome is not immune-mediated, contrary to Dr. Bellanti's entire presentation, although Dr. Bellanti admitted that the concept of nephrotic syndrome was changing "as we speak." This change is discussed in the Greenbaum paper. The undersigned finds Dr. Kaplan's extraordinary experience and training in pediatric nephrology to be more credible than Dr. Bellanti's experience as an immunologist. Moreover, Dr. Bellanti stated he relied on imagination to posit his thesis that cytokines stimulated from flu vaccinations adversely affected J.M.'s kidneys.

Once the medical theory that flu vaccine caused an innate immune reaction followed by an adaptive immune response becomes irrelevant to the current understanding of minimal change nephrotic syndrome, the linchpin of petitioner's allegations disappears and we are left with no

persuasive medical theory linking the 2009 flu vaccination to J.M.'s second relapse of minimal change nephrotic syndrome, subsequent relapses, and three cerebral arterial strokes.

The evidence is persuasive that J.M.'s five-pound increase in weight the morning of October 1, 2009 heralded the onset of the relapse of his nephrotic syndrome. The issue then is whether or not flu vaccine, which he received later that day after he finished school, significantly aggravated his ongoing relapse. Moreover, the issue of J.M.'s strokes is an enigma that neither Dr. Quan nor Dr. Kaplan could explain in terms of sequelae.

The Federal Circuit in Capizzano v. Sec'y of HHS, 440 F.3d 1317, 1326 (Fed. Cir. 2006), emphasized that the special masters are to evaluate seriously the opinions of petitioner's treating doctors since "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." See also Broekelschen v. Sec'y of HHS, 618 F.3d 1339, 1347 (Fed. Cir. 2010); Andreu v. Sec'y of HHS, 569 F.3d 1367, 1375 (Fed. Cir. 2009). The undersigned considers seriously the opinion of Dr. Quan, J.M.'s second pediatric nephrologist. He succinctly described the problem with understanding minimal change nephrotic syndrome in his expert report (Ex.40, at 3), as follows:

> So, where does the truth about the cause of minimal change nephrotic syndrome lie? Does the immune system play a major role or can this role be relegated to other causes? The actual truth may lie in the fact that nephrotic syndrome may have different underlying causes in different patients. Newer mechanisms of nephrotic syndrome, therefore[,] do not preclude an important role for the immune system in many patients. However, such differences in the underlying causes to the nephrotic syndrome may explain why a "one size fits all" conventional treatment regimen is not effective in all patients.

Dr. Quan's statement is the crux of this case. Not all minimal change nephrotic syndrome is the same. Dr. Bellanti explained that the reason this is called a "syndrome" and not a "disease" is that it has many forms and these forms are not all the same. Dr. Quan stressed that minimal change nephrotic syndrome differs in adults and in children. It probably differs from child to child as doctors can diagnose a cause in some children, but in J.M., Dr. Seikaly, J.M.'s first pediatric nephrologist, could not identify any cause and diagnosed J.M. with idiopathic minimal change nephrotic syndrome. The undersigned's responsibility therefore is to determine what kind of minimal change nephrotic syndrome J.M. had. The Federal Circuit in Broekelschen v. Sec'y of HHS, 618 F.3d 1339, 1346 (Fed. Cir. 2010), stated "identifying the injury is a prerequisite to the analysis."

Before the onset of J.M.'s minimal change nephrotic syndrome in September 2007, J.M. had had nine illnesses varying from colds to infections, and 26 vaccinations, including FluMist on November 20, 2006. None of these illnesses (including viruses) and vaccinations (including attenuated live virus flu vaccine) precipitated the onset of J.M.'s minimal change nephrotic

syndrome.

After the onset of J.M.'s nephrotic syndrome, he had remission with tapering of steroids on December 19, 2007 followed by full remission and being off prednisone on February 6, 2008. Before his second relapse on June 10, 2009, he had a cold on January 15, 2008. He received his second Varivax on July 28, 2008 and his first killed virus flu vaccine on November 19, 2008. None of these possible triggers, i.e., the cold and the two vaccinations, precipitated J.M.'s first relapse of minimal change nephrotic syndrome on June 10, 2009.

One could safely conclude at this point that exposure to antigens in either live virus or killed virus form or in the form of infections including colds did not constitute a trigger to J.M.'s onset or first relapse of minimal change nephrotic syndrome.

Petitioner and his wife are devoted parents who methodically and carefully kept a calendar each day recording around 7:30 a.m. each day (except later on weekends) J.M.'s urine (to see if it contained protein), weight, and blood pressure. Petitioner made the readings and either he or his wife wrote the numbers in the calendar. J.M.'s first pediatric nephrologist Dr. Seikaly told petitioner and his wife on August 26, 2009 that if proteinuria or edema returned, petitioner and his wife were to call the nephrology clinic. Edema was important to Dr. Seikaly.

When petitioner was testifying, petitioner's counsel drew to his attention that J.M. had a five-pound weight gain (from 119 pounds on September 30, 2009 to 124 pounds on October 1, 2009) before J.M. received flu vaccine later in the day around 3:30 p.m. or 4:00 p.m. Petitioner then testified that there were numerous reasons to regard the weight gain as meaningless: (1) he did not know if J.M. had weighed himself and just called out the weight; (2) he did not know whether petitioner had taken J.M.'s weight in the morning or later that day; (3) he did not know whether or not J.M. was wearing clothes when he was weighed that day; (4) he did not know whether or not J.M. had eaten before he was weighed; and (5) he did not know how accurate or inaccurate the scale was or even which scale was used. This backpedaling did not enhance petitioner's credibility.

None of us knows more than petitioner was willing to reveal because all we have is the calendar which recorded negative protein on October 1, 2009 but a five-pound weight gain since the day before. What we do know is that the weight gain occurred on the same day as the vaccination at issue, and that J.M. continued to gain weight during the month of October 2009 to the extent that he was 28 pounds heavier on October 29, 2009 than he had been at the end of September. It is conceivable that petitioner did the protein test in J.M.'s urine earlier than weighing J.M. October 1, 2009 which would explain how the protein test was negative when J.M. was putting on weight. The only conclusion that the undersigned can draw is that J.M.'s second relapse of minimal change nephrotic syndrome either began before he received his flu vaccination on October 1, 2009, simultaneously with the vaccination, or within 16 hours of the vaccination when petitioner measured the protein in J.M.'s urine on October 2, 2009 and it was plus 3, meaning proteinuria. Any of those three onsets is problematic for petitioner prevailing in this case.

Dr. Bellanti made an extensive effort to prove that J.M.'s prior flu vaccinations, including the intranasal FluMist in 2006 and the killed virus flu vaccination in 2008, created an anamnestic effect so that J.M. reacted within one day to his second killed virus flu vaccination on October 1, 2009. When respondent helpfully filed Exhibit T which listed the components of these flu vaccines, which are not identical, Dr. Bellanti stated that identical components were unnecessary. The undersigned does not find Dr. Bellanti's opinion credible. The undersigned realizes there are extensive case reports filed in this case which posit that various vaccinations (mostly but not all in adults) caused their nephrotic syndrome (which was not necessarily minimal change), but these case reports are speculating as to cause. The undersigned also realizes that the medical community has fastened upon the idea in the past that minimal change nephrotic syndrome is an immune-mediated (although not autoimmune) disease which explains why steroids such as prednisone are used to treat the disease, in most cases successfully. But the undersigned credits Dr. Kaplan's testimony over Dr. Bellanti's. Dr. Kaplan is a remarkably accomplished and experienced pediatric nephrologist. Greenbaum's article supports Dr. Kaplan's thesis that viewing minimal change nephrotic syndrome as immune-mediated is no longer the current medical view, although articles such as Franklin's still are published asserting that it is. Dr. Levinson, respondent's immunologic expert, also supported the current view that both the innate and adaptive immune systems are irrelevant when speaking of minimal change nephrotic syndrome. Dr. Quan, who testified both as treating and expert pediatric nephrologist, admitted that minimal change nephrotic syndrome may have different causes in different patients.

Dr. Quan also made some other important admissions. He said that it was impossible to say if a flu shot would make a relapse already in progress worse (although it might) because there was no evidence that that would be the case. Tr. at 66. He admitted that weight gain is a sign or symptom of a relapse of nephrotic syndrome. Tr. at 74-75, 76. He said he could not say if the flu vaccine worsened J.M.'s course of nephrotic syndrome. Tr. at 78. He said one does not really know if there is a natural course of minimal change nephrotic syndrome--"nobody has a crystal ball to tell you exactly how well they're going to do." Tr. at 225.

Even Dr. Bellanti made some important admissions. He said that innate immune injury may be playing a role in the pathogenesis of J.M.'s condition. Tr. at 134. "May" means "possible" which does not satisfy petitioner's burden of proof of preponderant evidence. Section 300aa-13(a)(1)(A). He also said that when he trained as a resident, minimal change nephrotic syndrome was a mystery and that its pathogenesis was now changing "as we speak." Tr. at 142. Dr. Bellanti's resort in rebuttal to quoting Einstein's emphasis on imagination being more important than knowledge reinforced in the undersigned's mind that Dr. Bellanti was speculating in his presentation of how the innate and adaptive immune systems not only explained how the October 1, 2009 flu vaccination triggered J.M.'s second relapse of minimal change nephrotic syndrome, but also in his explanation that an anamnestic response caused the rapid onset of proteinuria within 16 hours of vaccination.

The undersigned does not accept that substances that are not identical can provoke an anamnestic response. When the undersigned sees this theory used in vaccine cases, it is always

of the same substance, such as repeated hepatitis B vaccinations, all of which are identical. Moreover, hepatitis B vaccines are given usually one month apart for the first two vaccinations and then a few months later for the third. Here, J.M. received the 2006 FluMist which had no component identical to the 2008 and 2009 killed virus flu vaccines two and three years later, and the 2008 flu vaccine had only two of three component strains identical to the 2009 flu vaccine one year later.

Moreover, since HHS added flu vaccine to the Vaccine Injury Table in 2005, the Office of Special Masters has seen innumerable flu vaccine/Guillain-Barré syndrome ("GBS") cases filed. If exposure to prior flu vaccines were to cause an anamnestic response, the special masters should be seeing earlier onset intervals among the elderly vaccinated with flu vaccine who contract GBS than among the young who would have received far fewer prior flu vaccinations than the elderly. No special master has ever commented on there being an abbreviated onset of GBS among the elderly flu vaccinees compared to younger vaccinees. When HHS made GBS a Table injury for flu vaccine, effective March 21, 20017, the onset interval of 3 to 42 days was not broken down into age categories on the premise that the elderly will always react quicker due to multiple prior exposures to flu vaccines. When Dr. Bellanti said in his rebuttal testimony that he is relying on imagination to put together an explanation that would prove J.M.'s October 1, 2009 flu vaccination caused his second relapse, the undersigned believes he was relying on speculation, rather than science or current medical consensus. The Federal Circuit does not permit the undersigned to rule for petitioner based on speculation, but on a persuasive scientific or medical theory. The undersigned finds Dr. Bellanti's testimony unpersuasive as it is not linked to current medical theory as Dr. Kaplan and Dr. Levinson explained.

The one mystery that the undersigned pursued with Dr. Kaplan and Dr. Levinson is why immune suppressants and anti-inflammatory drugs can successfully treat minimal change nephrotic syndrome in most cases, yet minimal change nephrotic syndrome is currently no longer medically accepted as immune-mediated but as a podocytopathy. Dr. Kaplan said that the steroids affected the podocytes and basement membrane through the Angiopoietin 4 chemical, which has nothing to do with immunologic factors, and this was an evolving subject. Dr. Levinson said that steroids were acting as anti-inflammatory agents but this had nothing to do with immune mediation as a mechanism. The undersigned finds their testimony credible.

Because I find that petitioner has failed to provide a persuasive scientific or medical theory proving that flu vaccine caused J.M.'s second relapse of minimal change nephrotic syndrome, further analysis should be unnecessary. However, for the sake of completeness, the undersigned does a Loving analysis:

(1) J.M.'s condition prior to the administration of flu vaccine was in remission of minimal change nephrotic syndrome after his first relapse;
(2) J.M.'s current condition is post-stroke residua but he no longer has minimal change nephrotic syndrome;
(3) J.M.'s current condition is significantly worse than his pre-October 1, 2009 condition;
(4) there is no persuasive medical theory causally connecting J.M.'s significantly

worsened current condition to the October 1, 2009 vaccination;

(5) there is no logical sequence of cause and effect showing that the October 1, 2009 vaccination was the reason for the significant worsening; and

(6) there is no persuasive showing of a proximate temporal relationship between the October 1, 2009 flu vaccination and the significant worsening as the undersigned finds that 16 hours is too brief an interval (assuming that the five-pound weight gain on October 1, 2009 does not mean the onset of the second relapse of J.M.'s minimal change nephrotic syndrome occurred before vaccination) even if minimal change nephrotic syndrome were immune-mediated and not a podocytopathy.

This case is dismissed for failure to make a prima facie case of causation in fact significant aggravation.

CONCLUSION

This petition is **DISMISSED**. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court is directed to enter judgment herewith.[40]

IT IS SO ORDERED.

Dated: June 28, 2018

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

[40] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party, either separately or jointly, filing a notice renouncing the right to seek review.