In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: June 23, 2016

* * * * * * * * * * * * * * *	PUBLISHED DECISION
GRZEGORZ RUS *and* AGNIESZKA RUS, *as parents and natural guardians of* A.R.,	No. 12-631V
	Special Master Gowen
Petitioners,	
	Denial of Entitlement;
v.	Hepatitis A (Hep A) Vaccine;
	Nephrotic Syndrome
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	

Kate G. Westad, Larkin Hoffman, et al., Ltd., Minneapolis, MN, for petitioners.
Amy P. Kokot, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

On September 25, 2012, Grzegorz and Agnieszka Rus ("petitioners"), filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or the "Program"),[2] 42 U.S.C. § 300aa-10 et seq. (2012), on behalf of their minor child, A.R. Petitioners alleged that as a result of receiving the Hepatitis A ("Hep A") vaccine on October 30, 2009, A.R. developed nephrotic syndrome. Petition at ¶ 1. Respondent recommended against awarding compensation to petitioners. Respondent's ("Resp.") Report at 2.

After a review of the entire record, I find that petitioners have failed to provide preponderant evidence that the Hep A vaccination A.R. received on October 30, 2009, caused her nephrotic syndrome. It may have caused her transient fever and seizure, but neither of those conditions had sufficient duration to qualify for a Program award. Accordingly, petitioners are not entitled to compensation.

[1] Because this published decision contains a reasoned explanation for the action in this case, I intend to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to delete medical or other information, the disclosure of which would constitute a clearly unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will delete such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

I. BACKGROUND

A. Procedural History

Petitioners filed their petition on September 25, 2012, alleging that A.R. developed nephrotic syndrome as a result of receiving the Hepatitis A vaccine on October 30, 2009. Petition at ¶ 1. Respondent filed her Rule 4(c) report advising against compensation on May 31, 2013.

Petitioners filed the expert report of Dr. Jan T. Kielstein, a nephrologist, on August 15, 2013, followed by the medical literature referenced in Dr. Kielstein's report on August 28, 2013. See Petitioner's ("Pet.") Exs. 12, 14-27. Respondent filed the expert report of Dr. Bernard S. Kaplan, a pediatric nephrologist, on November 12, 2013, along with the medical literature referenced in his report. See Resp. Ex. A. Petitioners filed a supplemental expert report from Dr. Kielstein on March 6, 2014, and a second supplemental report from Dr. Kielstein on June 27, 2014, followed by the medical literature referenced in the reports on July 3, 2014. See Pet. Exs. 30-35. Respondent filed a supplemental expert report from Dr. Kaplan on September 12, 2014. See Resp. Ex. C.

An entitlement hearing was held on Thursday, September 17, 2015, in Washington, D.C. Agnieszka Rus and Dr. Kielstein testified on behalf of petitioners, and Dr. Kaplan testified on behalf of respondent. Petitioners filed their post-hearing brief on December 14, 2015, and respondent filed her post-hearing brief on February 16, 2016. This matter is now ripe for adjudication.

B. Summary of Relevant Facts

A.R. was born on August 31, 2006. Pet. Ex. 1. Between birth and 2009, A.R.'s growth and development were normal. See generally, Pet. Ex. 4 at 4-46. A.R. made a sick visit to her pediatrician on June 22, 2009, with a congested nose, fever, and cough. Id. at 45. She was not prescribed antibiotics. See id. On October 30, 2009, A.R. returned to her pediatrician for her three-year well-child visit. Id. at 47. At that visit, she was noted to be a healthy child with normal development, and no notation was made of any upper respiratory infection. Id. A.R.'s mother testified that A.R. was healthy, happy, and energetic prior to October 30, 2009. Tr. at 9. Mrs. Rus also testified that in the days and weeks leading up to the October 30, 2009, visit, A.R. did not have any foamy urine or odor to her urine. Id. at 11. At the October 30, 2009, pediatrician visit, she was administered a Hepatitis A vaccine. Pet. Ex. 4 at 47. This was the first Hep A vaccine she received. See Pet. Ex. 2 at 1.

Late the next day, on October 31, 2009, A.R. was taken to the emergency room at Stamford Hospital. Pet. Ex. 3 at 43. According to the emergency medical services record, A.R. was "found lethargic supine on floor of residence . . . Mom states pt with 101 fever, gave Tylenol and put pt to bed . . . Mom states pt woke up and was shivering." Id. In the emergency department, rhinorrhea and cough were checked on review of systems. Id. at 26. No edema was noted. Id. at 44. The discharge summary from Stamford Hospital on November 1, 2009, summarizes:

> She started having fevers today, the highest was 102.2, and then the parents noticed that she had an episode where she was shaking all over

> her body with her eyes rolled back into her head, lasted about a minute. She has never had this before. The child had a little bit of runny nose, a little bit of dry cough. She vomited once after getting Tylenol at home. She was given hepatitis B[3] vaccine 2 days ago at the pediatrician's office.

Pet. Ex. 3 at 46. On physical examination, her temp was 40.1 (104.1 F), pulse was 159, and she was saturating 98% on room air. Id. She had "[c]lear breath sounds bilaterally. No wheezes, no crackles." Id. The record states "I suspect that the child had a febrile seizure tonight, which was brought on by the fever, which is likely secondary to her being vaccinated 2 days ago." Id.

Laboratory results of blood and urine collected on November 1, 2009, revealed that A.R.'s albumin was normal (3.7 [ref 3.2-4.8 g/dL]), her total blood protein was slightly decreased (6.1 [ref 6.4-8.3 g/dL]), and her urine protein was elevated (> = 300 [ref negative mg/dL]). Pet. Ex. 3 at 49. Her white blood count was normal. Id. at 48. A chest x-ray was normal. Id. at 45. A nasal swab for influenza was negative. Id. at 49.

On November 1, 2009, A.R. was seen for follow-up at her pediatrician's office. Pet. Ex. 4 at 49. On exam, A.R. was found to have a "wet cough" and the impression was "URI [status post] 1st febrile [seizure]." Id. A.R. returned to the pediatrician on November 4, 2009, and was noted to have a "swollen face" but no fever or cough, although nasal congestion and cough were checked as present on the physician's review of symptoms. Id. at 51. Lab work on November 4, 2009, revealed that she had decreased albumin (2.9 [ref 3.2-4.8 g/dL]), markedly decreased total blood protein (4.8 [ref 6.4-8.3 g/dL]), marked proteinuria (481.2 [ref <12 mg/dL]), and high triglycerides (301 [ref <150 mg/dL]) and cholesterol (329 [ref <170 mg/dL]). Pet. Ex. 3 at 78-79. A second chest x-ray was performed and was again normal. Id. at 77. Her white blood count was again normal. Id. at 78. The following day, on November 5, 2009, A.R.'s pediatrician indicated that her facial swelling had decreased. Id. at 53. At another follow-up appointment on November 9, 2009, A.R. was not swollen and was "feeling a little better but now [had been] coughing since Sat. [November 7]," and a "deep chesty cough" was observed. Id. at 55. She was referred to a nephrologist for evaluation of nephrotic syndrome. Id.

On November 11, 2009, A.R. was seen for a consultation at Yale University's Division of Pediatric Nephrology by Dr. Jeff Stein. See Pet. Ex. 5. Dr. Stein's summary states that the impression was "[p]resentation consistent with idiopathic nephrotic syndrome, likely minimal change disease likely triggered by her recent respiratory tract infection which in retrospect was likely viral as it is improving without specific therapy." Id. at 2-3. She was started on prednisone. Id. at 3. A renal biopsy was not performed. Genetic testing for PLCE1, podocin, ACTN4, TRPC6, and INF2 were negative. Id. at 108. Her family history is also negative for known renal disease. Id. at 2. A.R. has since had multiple relapses of her nephrotic syndrome.

II. STANDARDS FOR ADJUDICATION

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system

[3] The emergency department record incorrectly states that A.R. received the hepatitis B vaccine. See Pet. Ex. 2 at 1.

as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

To receive compensation under the Program, petitioners must prove either a "Table" injury[4] or a causation-in-fact injury, i.e. that a vaccine listed in the Table was the cause in fact of an injury (an "off-Table" injury). See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioners allege A.R. suffered an "off-Table" injury. Therefore, petitioners must demonstrate by preponderant evidence that a covered vaccine is responsible for A.R.'s injury.

An "off-Table" injury is initially established when the petitioner demonstrates by a preponderance of the evidence: (1) she received a vaccine set forth on the Vaccine Injury Table; (2) she received the vaccine in the United States; (3) she sustained or had significantly aggravated an illness, disease, disability, or condition caused by the vaccine; and (4) the condition has persisted for more than six months. § 13(a)(1)(A). To satisfy her burden of proving causation in fact, petitioner must establish each of the three Althen factors 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 proximate temporal relationship between vaccination and injury. Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005); see de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each Althen factor must be established by preponderant evidence). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

The Federal Circuit in Althen noted that "while [Althen's petition] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a *sequence hitherto unproven in medicine,* the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body."* Althen, 418 F.3d at 1280 (emphasis added).

Once petitioner establishes each of the Althen factors by preponderant evidence, the burden of persuasion shifts to respondent, who must show that the alleged injury was caused by a factor unrelated to the vaccination. Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994); § 13(a)(1)(B). Respondent must demonstrate that "the factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated do "not include any idiopathic, unexplained, unknown,

[4] A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

In determining whether petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Thus a special master must weigh and evaluate opposing expert opinions, medical and scientific evidence, and the evidentiary record in deciding whether petitioners have met their burden of proof. "Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu v. Sec'y of HHS, 569 F.3d 1367, 1380 (Fed. Cir. 2009) (referencing Althen, 418 F.3d 1274; Capizzano, 440 F.3d 1317).

III. EXPERT OPINIONS

A. Nomenclature

The parties agree that A.S. was diagnosed with nephrotic syndrome ("NS") and had full blown NS by November 4, 2009. Joint Pre-Hearing Submission at 1; Tr. at 47-48; Resp. Ex. A at 2. The major manifestations of NS include proteinuria, hypoalbuminemia, edema, hyperlipidemia, and lipiduria. Resp. Ex. A-23[5] at 1. As Dr. Kielstein explained, in the kidney, the glomerular basement membrane ("GBM") keeps proteins in the blood from being spilled into the urine. Tr. at 76. The GBM is a complex layer comprised of several different types of cells and cell layers, including podocytes, foot processes and epithelial cells, which function to prevent protein in the blood from passing into the urine. Id. at 76-77. In NS, there is a breakdown in the basement membrane or in the podocytes. Id. at 78-80.

In their respective expert reports, Dr. Kielstein characterized A.S.'s nephrotic syndrome as "minimal change nephrotic syndrome" whereas Dr. Kaplan characterized it as "steroid sensitive nephrotic syndrome." Pet. Ex. 12 at 4; Resp. Ex. A at 2. Later, Dr. Kaplan stated that "[i]diopathic nephrotic syndrome is also known as steroid-sensitive nephrotic syndrome ["SSNS"] as well as minimal change nephrotic syndrome [MCNS]." Resp. Ex. A at 3. Dr. Kielstein agreed that the terms minimal change nephrotic syndrome, steroid sensitive nephrotic syndrome and idiopathic nephrotic syndrome are often used interchangeably. Pet. Ex. 30 at 2. Dr. Kielstein testified that a diagnosis of SSNS in A.R.'s case is technically "more correct," because a diagnosis of MCNS requires a renal biopsy, which A.R. did not have. Tr. at 53-55. However, he added that in children, NS that responds to steroids is almost always MCNS (about 90% of the time), so biopsies are not typically performed. Id. at 51, 55. Dr. Kaplan stated that a renal biopsy is *never* indicated in a child who presented with classical features of nephrotic syndrome, no poor prognostic findings, and a rapid response to steroids. Resp. Ex. A at 4. Dr. Kielstein said that there is no difference, in terms of the analysis of causation, between "minimal change nephrotic syndrome" and "steroid sensitive

[5] Resp. Ex. A-23, Lionel C. Clement et al., *Podocyte Secreted Angiopoietin-Like-4 Mediates Proteinuria in Glucocorticoid Sensitive Nephrotic Syndrome*, 17(1) NAT. MED. 117 (2011).

nephrotic syndrome," and Dr. Kaplan stated that the difference is really just pedantic. Tr. at 55-56; Resp. Ex. C at 2. In short, the experts agree that the varying nomenclature described the same disease process in almost all pediatric cases. Thus, A.R.'s nephrotic syndrome is referred to as MCNS or NS throughout this decision.

B. Expert Testimony

i. Petitioners' Expert, Dr. Kielstein

Dr. Kielstein was admitted as an expert in the field of nephrology. Tr. at 24. He is a board certified internist and nephrologist. Id. at 18. Dr. Kielstein obtained his medical degree at the University of Magdeburg, Germany, in 1995. Id. at 16. During medical school, he worked in the Pediatric Department at the floating hospital at Tufts University, doing pulmonary pediatrics, and did a year of biomedical research at the Shriner's Hospital for Children in Tampa, Florida. Id. at 16-17. He obtained a PhD (Medicine) in 1999 from Hannover Medical School. Pet. Ex. 13 at 1. He served his residency and fellowship at the Hannover Medical School, where he then became an internist and nephrologist. Id. at 18. From 2004 to 2007, he did a post-doctoral fellowship in the Vascular Biology Program at Stanford University Medical Center. Pet. Ex. 13 at 2.

Dr. Kielstein returned to Germany and became an assistant professor of medicine in the Department of Internal Medicine, Division of Nephrology and Hypertension at the Hannover Medical School. Pet. Ex. 13 at 2. In this role, he works mainly in the acute nephrology setting, but oversees a spectrum of nephrology. Tr. at 19. He also recently became head of the Nephrology and Hypertension Department at the tertiary care hospital in Braunschweig, an associate teaching hospital of the Hannover Medical School. Id. In his nephrology practice at the Hannover Medical School, he sees patients with all chronic kidney diseases for diagnosis and special treatment. Id. His department is responsible for treating acutely ill children with extracorporeal treatment, and as medical director, Dr. Kielstein consults on the pediatric patients and takes over their treatment once they turn 16. Id. at 20-21. The adult and pediatric departments also have a joint weekly conference on renal biopsies. Id. Dr. Kielstein is associate editor at the European journal *Nephrology Dialysis and Transplantation*, and is responsible for the section on acute kidney injury. Id. at 22. He has also served as an expert on various panels, testifying before the European Medical Agency and a panel of the European Dialysis and Transplant association. Id. at 23-24.

Dr. Kielstein opined that the Hepatitis A vaccination caused A.R.'s nephrotic syndrome. See Pet. Ex. 12 at 11. He explained that the Hep A vaccine is made of inactivated hepatitis A virus (along with other components added to make the inactivated virus stay longer and allow the immune system to respond), to which the immune system responds by producing antibodies. Tr. at 58-59. In addition to acquiring immunity to hepatitis A as intended, Dr. Kielstein stated that there can be adverse immunological reactions to vaccine, where the immune response triggers immunological disease in individuals with a susceptible underlying genetic background. Id. at 59-60.

Dr. Kielstein set forth two possible mechanisms for the etiology and pathogenesis of nephrotic syndrome: (1) a "specific" T-cell response, and (2) an inflammatory cytokine response to the vaccination that alters an "unspecific" pathway, involving angiopoietin-like 4. Tr. at 86, 117.

First, he proposed that MCNS could be caused by a "specific" T-cell response to vaccination where systemic T-cell dysfunction results in the production of a circulating glomerular permeability factor, which directly induces podocyte foot process fusion. Pet. Ex. 12 at 5. The foot process fusion would severely alter the glomerular filter system, resulting in proteinuria. Id.

Second, Dr. Kielstein proposed that MCNS could be initiated through an "unspecific" inflammatory pathway—a cytokine response to the vaccination that alters the production (in quality and quantity) of angiopoietin-like 4 (ANGPTL4), a structure expressed in the podocytes that is important to the podocyte function of keeping proteins in the blood. Pet. Ex. 31 at 2; Tr. at 77-78. Overproduction in podocytes of a form of ANGPTL4 lacking sialic acid residues would cause binding of ANGPTL4 to the glomerular basement membrane, diffuse effacement of foot processes and loss of glomerular basement membrane electric charge, thereby inducing the development of nephrotic-range proteinuria. Pet. Ex. 30 at 3. Dr. Kielstein testified that this "unspecific" pathway is not T-cells,[6] but rather is a separate mechanism that occurs in response to inflammation in the body. Tr. at 79. He did not provide an explanation as to how vaccination would trigger the alteration in ANGPTL4 production, but said "[a]ll that we know about angiopoietin-like 4 is that it can unspecifically be altered in terms of both production and kind of linking the sugar side chains to the core structure." Tr. at 80-81.

In addition to the two mechanisms set forth above, Dr. Kielstein stated in his written report that antibodies and B-cells "can in general be involved in the pathophysiology of [MCNS]" and are "one of several mechanisms leading to [MCNS]." Pet. Ex. 30 at 3-4. In support of this, he cited several studies looking at the effect of Rituximab, an anti-CD20 agent, in patients with relapsing or steroid resistant MCNS. Id. [7]

To support his opinion that vaccines can cause MCNS, Dr. Kielstein noted that there are "several anecdotal reports linking MCNS to vaccinations." Pet. Ex. 12 at 5 (citing Pet. Exs. 15-20, 27[8]). The articles cited report MCNS after hepatitis B, pneumococcal, influenza, tetanus-diphtheria,

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[6] Although he made a distinction at hearing between a T-cell mechanism and an ANGPTL4 mechanism, Dr. Kielstein's third expert report states that "cross-talk" between T-cells and dendritic cells that results in the production of intrarenal cytokines would alter the production of ANGPTL4 and "T-cell mediated reaction to the vaccine is likely the cause" of ANGPTL4 alteration. Pet. Ex. 31 at 2.

[7] The articles cited by Dr. Kielstein in his supplemental expert report as references 4-7 were not filed as exhibits. See Pet. Ex. 30 at 10. Respondent's Exhibit A-24 discusses Rituximab. Resp. Ex. A-24, Larry A. Greenbaum et al., Childhood Nephrotic Syndrome—Current and Future Therapies, 8 NATURE REVIEWS NEPHROL 445 (2012).

[8] Pet. Ex. 15, Sila Ozdemir et al., *Nephrotic Syndrome Associated With Recombinant Hepatitis B Vaccination: A Causal Relationship or Just a Mere Association?*, 13 NEPHROLOGY DIALYSIS TRANSPLANTATION 1888 (1998); Pet. Ex. 16, F. Macario et al., *Nephrotic Syndrome After Recombinant Hepatitis B Vaccine*, 43 CLINICAL NEPHROLOGY 349 (1995); Pet. Ex. 17, Ismail Islek et al., *Nephrotic Syndrome Following Hepatitis B Vaccination*, 14 PEDIATRIC NEPHROLOGY 89 (2000); Pet. Ex. 18, Y. Kikuchi et al., *Minimal Change Nephrotic Syndrome, Lymphadenopathy and Hyperimmunoglobulinemia After Immunization with a Pneumococcal Vaccine*, 58 CLINICAL NEPHROLOGY 68 (2002); Pet. Ex. 19, J.T. Kielstein et al., *Minimal Change Nephrotic Syndrome in a 65-Year-Old Patient Following Influenza Vaccine*, 54 CLINICAL NEPHROLOGY 246 (2000); Pet. Ex. 20, Christian Clajus et al.. *Minimal Change Nephrotic Syndrome in an 82 Year Old Patient Following a Tetanus-Diphtheria-Poliomyelitis-Vaccination*, 10:21 BMC

poliomyelitis, and smallpox vaccinations. Id. He said that the fact that a variety of vaccines "have been linked to minimal-change nephrotic syndrome. . . is important because it tells us that it is not the—one specific vaccine. . . but it's, rather, a general response to the vaccination that is then obviously, in a few patients, triggering the disease." Tr. at 64. However, he admitted that the existing literature was a "low-quality database," as the studies are not "prospective, randomized studies." Id. at 65.

With regard to the Hep A vaccine specifically, Dr. Kielstein cited a case report of a man who allegedly developed autoimmune hepatitis after receipt of a hepatitis A vaccine.[9] Id. at 68-69. On cross-examination, he admitted that he was not aware of any case reports showing the development of nephrotic syndrome following a Hep A vaccine, and he was not aware of any medical literature where the authors assert a causal connection between Hep A and nephrotic syndrome. Id. at 118.

Dr. Kielstein also cited studies finding that vaccinations (meningococcal conjugate & hepatitis B) have been found to trigger relapses in children with *established* MCNS. Pet. Ex. 12 at 6 (citing Pet. Exs. 25, 26[10]).[11] He admits, however, that "scarce evidence links various vaccinations to the newly developed MCNS." Id. Dr. Kielstein also cited studies finding lupus nephritis and necrotizing glomerulonephritis following hepatitis B and influenza vaccinations, respectively. Id. (citing Pet. Exs. 23, 24[12]); Tr. at 64.

ii. Respondent's Expert, Dr. Kaplan

Dr. Kaplan was admitted as an expert in the field of pediatric nephrology. Tr. at 129. Dr. Kaplan received his medical degree from the University of Witwatersrand in Johannesburg in 1964. Resp. Ex. B at 1. He then trained as a pediatrician, passed the fellowship of the College of Physicians in South Africa, and obtained a diploma in pediatrics. Tr. at 119-20; Resp. Ex. B at 1. He trained in pediatric nephrology in Montreal from 1970 to 1975 (with the exception of a year where he trained as a fellow in internal medicine). Tr. at 120. He was the director of pediatric

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NEPHROLOGY (2009); Pet. Ex. 27, M.J. Chamberlain et al., *Oliguric Renal Failure in the Nephrotic Syndrome*, 35 QJ MED 215 (1966).

[9] Pet. Ex. 27, P.A. Berry & G. Smith-Laing, *Hepatitis A Vaccine Associated with Autoimmune Hepatitis*, 13 World J. Gastroenterology 2238 (2007).

[10] Pet. Ex. 25, A.S. Abeyagunawardena et al., *Risk of Relapse After Meningococcal C Conjugate Vaccine in Nephrotic Syndrome*, 362 LANCET 449 (2003); Pet. Ex. 26, I. Szajner-Milart et al., *Efficacy of Vaccination Against Viral Hepatitis Type B in Children with the Nephrotic Syndrome*, 58(1) ANN UNIV MARIAE CURIE SKLODOWSKA MED. 402 (2003).

[11] Dr. Kielstein's report, Pet. Ex. 12, also cites references 17 and 18, which do not appear in the list of references appended to the report.

[12] Pet. Ex. 23, D. Santoro et al., *Lupus Nephritis After Hepatitis B Vaccination: An Uncommon Complication*, 67 CLINICAL NEPHROLOGY 61 (2007); Pet. Ex. 24, L. Hyla-Klekot, G. Kucharska, & W. Cieslak, *Necrotizing Glomerulonephritis in Decursu Vasculitis After Vaccination Against Influenza*, 19(109) POL MERKUR LEKARSKI 75 (2005).

residency training at McGill University for nine years, and was the chief of the renal service and renal laboratory at Montreal Children's Hospital for seven years. Id. at 120.

Beginning in 1987, he held the position of chief of nephrology at the Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania for twenty-two years. Tr. at 120-21. At CHOP, he established the dialysis program and the renal transplant program. Id. at 120. He is currently a professor of pediatrics, professor of medicine, and professor of neurology at the University of Pennsylvania. Id. He is board certified in pediatrics and pediatric nephrology, and continues to work as a consultant nephrologist in the outpatient setting, seeing patients three days a week, primarily pediatric. Id. at 121-22. Over the course of his career, he has treated several hundred children with nephrotic syndrome. Id. at 122-23. He has authored approximately twenty-six publications on nephrotic syndrome, and is a reviewer for several journals, including *Pediatric Nephrology* and *Journal of Pediatrics*. Id. at 124.

Dr. Kaplan did not agree that the hepatitis A vaccine caused A.R.'s minimal change nephrotic syndrome. See Resp. Ex. A at 8. He recognized that the medical literature contained various hypotheses about the causal mechanism in nephrotic syndrome but opined that its cause and the nature of the permeability factor remained unknown. See Tr. at 142-45. He also recognized that there were several case reports suggesting temporal relationships between vaccines and nephrotic syndrome, but indicated that the number was very small in light of the large number of vaccines administered and did not involve hepatitis A vaccine in particular. Id. at 132, 156-58. He said that they do see relapses of nephrotic syndrome after upper respiratory infections or viruses, but have never been able to identify a specific virus as a trigger. Id. at 139-42. In addition, he would not testify that the possible upper respiratory infection A.R. had, as evidenced by a runny nose and slight cough, was the cause of her minimal change disease any more than he would testify that the vaccine caused it. Id. at 142.

IV. EVALUATION OF THE EVIDENCE[13]

All three prongs of Althen are at issue in this case. Therefore, the legal issues to be resolved are whether petitioners have put forth preponderant evidence of: (1) "a reliable medical theory causally connecting A.R.'s hepatitis A vaccination with her nephrotic syndrome;" (2) "a logical sequence of cause and effect showing that A.R.'s hepatitis A vaccination was the reason for her nephrotic syndrome;" and (3) "a proximate temporal relationship between A.R.'s hepatitis A vaccination and her nephrotic syndrome." Joint Submission at 2.

Althen Prong I requires petitioners to set forth a reliable medical theory explaining how the received vaccines could have caused the alleged injury. Althen, 418 F.3d at 1278. While scientific certainty is not required to establish causation under the Vaccine Act, the theory must be support by a "sound and reliable" medical or scientific explanation. Knudsen, 35 F.3d at 548. Furthermore, under Althen Prong III, the onset of the condition or its aggravation must have occurred in an appropriate time frame to enable its attribution to the vaccine. Althen, 418 F.3d at 1278. Thus, the onset or aggravation must have occurred after receipt of the vaccine within a time frame that can appropriately be explained by a reasonable medical explanation of the immune response. In this

[13] I have considered the entire record in arriving at my decision (§ 300aa–13(a)(1)). This includes extensive medical literature submitted by both parties, which I have read and considered. I will discuss in the course of this opinion the exhibits that are most relevant to the resolution of this case.

case, I find it appropriate to analyze the Althen Prongs in reverse order, beginning with the timing issue.

A. Althen III

The experts agreed that A.R. had full blown, diagnosable minimal change nephrotic syndrome by the November 4, 2009, follow up appointment, five days post-vaccination. Tr. at 47-48; Resp. Ex. A at 2. By this time, A.R. displayed all of the classic components of nephrotic syndrome. She had increased protein spilling into her urine, and the albumin in her blood was low, which led to the diffusion of fluid into her tissues and the swelling in her face. Pet. Ex. 3 at 78-79. She also had high triglycerides and cholesterol, which in this context are most often caused by lack of protein in the blood. Id.; Tr. at 45. Thus, as Dr. Kielstein testified, A.R.'s condition changed from no evidence of any kind of kidney disease through October 30, 2009, to relatively mild proteinuria fortuitously recognized on November 1, 2009, because of the workup she received for a fever and possible febrile seizure, to classical nephrotic syndrome with facial edema and albuminemia on November 4, 2009.

The analysis of Althen Prong III in this case involves three issues: (1) was the post-vaccination presentation a new onset of the disease; (2) if so, when after vaccination did the disease actually begin; and (3) could the disease progress from new onset to full blown nephrotic syndrome as rapidly as it did in this case. Dr. Kielstein persuasively argued that A.R. had no evidence whatsoever of renal disease prior to October 30, 2009, and his testimony was supported by that of Mrs. Rus. See e.g. Tr. at 47-48; 11-12. Dr. Kaplan, while acknowledging the disease progression in the time period post-vaccination, testified that it is impossible to know when nephrotic syndrome actually starts because it is typically not recognized until a child develops visible edema. Tr. at 137-38. But he said that in relapsing patients he has followed, he has provided the mothers with a bottle of Albustix and told them to check the child's urine once a week to see how things are going, or if the child has a viral infection or fever. Id. at 133. He said the mothers would often report 1+ or 2+ proteinuria before the child had any other symptoms. Id. Thus, he could not say whether A.R. had any proteinuria on October 29, 2009, but he also could not state that Dr. Kielstein was incorrect about the post-vaccine onset. Id. at 162-65. Despite this reservation, on the facts of this case, I find it reasonable to conclude that it is more likely than not that the child suffered a new onset of minimal change nephrotic syndrome during the post-vaccination time period.

The second timing issue is when after the October 30, 2009, vaccination A.R.'s nephrotic syndrome began. Both experts agreed that she had classical MCNS by November 4. Tr. at 47-48; Resp. Ex. A at 2. But that agreement left open the question of whether the initial proteinuria reading on November 1, when the other necessary components of minimal change disease were not present, represented the beginning of the syndrome. Dr. Kielstein acknowledged that it seems very likely that there was some breakdown of the basement membrane or the podocytes by November 1, and that that was the starting point of the disease. Tr. at 89. This conclusion becomes important under Althen Prong 1, as Dr. Kielstein also acknowledged that if the mechanism of nephrotic syndrome causation were purely a T-cell phenomenon, it would take a couple of days for the T-cell response to occur. Id. at 73-74. He agreed, in response to my question, that under our current understanding it would take more than a day or two to trigger a T-cell response. Id. at 75. He said the shortest time to generate such a response, based on the influenza report, is about 4 days. Id.

(referencing Pet. Ex. 19[14]). Importantly, however, he explained that nephrologists have learned in recent years that inflammation can disturb production of the substance known as angiopoietin-like 4 that is present in podocytes, and when that occurs protein can begin spilling into the urine within 24 hours. Id. at 77-79. Thus the timing of the T-cell theory appears problematic, but if the angiopoietin-like 4 theory is sustainable (see discussion below) this second question can be answered in the affirmative.

The third timing issue is whether nephrotic syndrome could progress from new onset to full blown nephrotic syndrome as rapidly as it did in this case. Dr. Kielstein explained that when NS occurs, there is a breakdown in either the basement membrane or the podocytes. Tr. at 78. He further explained that there is a sugar side and a celiac side on the podocytes, and that if you disrupt the sugar side, proteinuria can be induced within 24 hours. Id. at 78-79. Dr. Kielstein proposed the disruption in angiopoietin-like 4 as a possible cause, and Dr. Kaplan did not present any disagreement as to whether the disease could progress from onset to full blown disease on five days. See Pet. Ex. 30 at 3; Tr. at 142-43. Dr. Kielstein testified that nephrotic syndrome can develop rather rapidly, in days, no matter what the cause. Tr. at 71. Thus, if a reasonable and consistent theory to explain the onset of nephrotic syndrome in children can be demonstrated, I would conclude that the timing of the onset of A.R.'s disease is reasonable.

B. Althen II

As stated above, there was no evidence A.R. had any pre-existing nephrotic disease or proteinuria, and there was a fairly rapid development of the disease between November 1 and November 4, 2009. Dr. Kielstein explained that for nephrotic syndrome to occur, there must be a disruption of the glomerular filter system caused by a fairly profound injury to the barrier that keeps proteins in the blood and stops them from leaking into the urine. Tr. at 72. He said the glomerular filter system can be disrupted in a very short period of time, as in hours and days, by different mechanisms. Id. There was no serious disagreement on this point between the experts. If anything, Dr. Kaplan's testimony may be mildly supportive, as he stated he has observed slightly elevated proteinuria in relapsing patients before they became symptomatic because he had instructed parents on how to monitor that condition. See id. at 134. In fact, he testified that it was common that a mother doing the Albustix test would call him and say her child had 1+ or 2+ protein in the urine but was not puffy, and then sometimes she would call back in a week or two when the child was edematous or swollen. Id. at 134-38. Thus, assuming a reasonably reliable theory to explain how the vaccine could cause the condition, the progression of the disease in this case appears to meet the logical explanation requirement of Althen Prong II.

C. Althen I

The major debate in this case revolved around the understanding of the cause of minimal change nephrotic syndrome and whether a vaccine, or in particular the Hepatitis A vaccine, could trigger the process that results in this condition. In weighing the testimony and other evidence in this case, it became clear that Dr. Kielstein and Dr. Kaplan did not seriously disagree with each other about the state of medical knowledge on this subject. Rather, their disagreement centered on the extent to which reasonably reliable medical opinions, sufficient to meet the more likely than not

[14] Pet. Ex. 19, J.T. Kielstein et al., *Minimal Change Nephrotic Syndrome in a 65-Year-Old Patient Following Influenza Vaccine*, 54 CLINICAL NEPHROLOGY 246 (2000).

threshold of this Program, could be rendered as to the theoretical basis of the etiology of nephrotic syndrome and the potential vaccine causation thereof.

Dr. Kaplan aptly characterized the state of knowledge in this area when he said that when he first became a pediatric nephrologist (in the 1970s) the holy grail was to find the pathogenesis of nephrotic syndrome. Tr. at 147. Today, he said, the holy grail in pediatric nephrology is to find the permeability factor. Id. at 145. He stated that in some forms of nephrotic syndrome an immune pathogenesis was felt likely. Id. at 147. But, he said, "with regard to antibodies and antigens in this particular disease, there is absolutely no evidence . . . that this is an antibody-mediated disease." Id. at 147-48. He testified that "most of these children, in fact, have very low IgG levels because they lose the IgG in the urine, but they do not have complement abnormalities, they do not have deposits of immunoglobulins or complements in the kidney." Id. at 147. He concluded that "[t]here is no evidence whatsoever, according to anything we know at this time about minimal-change nephrotic syndrome and antibody-mediated disease, that this is an antibody-mediated disease." Id. at 147-48.

Dr. Kielstein did not disagree that there remains much to understand about the causal mechanism of minimal change disease, to say nothing of the potential of a vaccine or a particular vaccine to stimulate the process. He testified that nephrologists have been struggling for decades to elucidate underlying mechanisms. Tr. at 114. He did however, explain the theories that currently have some credence in the medical profession. He said that he believed that we cannot narrow it down to a single mechanism that causes this disease and that may explain the basis for vaccine causation. Id. at 114-15. He argued that the cause of nephrotic syndrome is most likely multi-factorial. Id.

Dr. Kielstein explained that there is a spectrum of reactions to vaccines. He said that you first have a local reaction, redness, a little swelling at the injection site, and ultimately have the intended adaptive immune response, mainly T-cell in the case of the Hepatitis A vaccine. Tr. at 115. Between those two responses is what he referred to as the "non-specific" or "unspecific" response[15] to the vaccination, which causes you to feel uncomfortable for the next day or more, secondary to cytokine release. Id. at 115-16. He opined that A.R.'s nephrotic syndrome could have been caused by a combination of the adaptive T-cell response and the inflammatory innate response that may have affected a substance known as angiopoietin-like 4. Id. at 116-17.

Dr. Kielstein explained that angiopoietin-like 4 is a structure found in the podocytes, which as noted above, contain a sugar side and a celiac side. He analogized angiopoietin-like 4 to a fence with barbed wire between the sugar side and the celiac side, which helps to keep the protein in the blood from going over to the urine side. Tr. at 76-79. Dr. Kielstein testified that the way the podocytes work to keep protein from spilling into the urine is very complex and involves the way they stick together and keep their shape. Id. at 78. He said that in recent years, angiopoietin-like 4 has received a lot of attention because it has been shown that disturbing one of two components of angiopoietin like-4 can very rapidly induce proteinuria, and the repair of the sugar side chains can reduce it in animals. Id. at 78-79. He explained that angiopoietin-like 4 is constantly being

[15] We were honored in this case to have expert testimony arriving in our court, at least indirectly, from distant shores—Dr. Kielstein coming from Hanover, Germany, and Dr. Kaplan from South Africa by way of more recent tenures in Montreal and Philadelphia. This led to some discussion of terminology, such as whether the term "impression" in a medical record meant "diagnosis" or something less. See, e.g. Tr. at 99, 141, 185. By the same token, Dr. Kielstein used the term "non-specific" or "unspecific" immune response in the way that I understand that we more often use the term "innate immune response."

produced at a certain rate and that both its production and linking to the sugar chains can be non-specifically altered and then the core structure does not work anymore. Id. at 80-81.

In support of this theory, Dr. Kielstein cited two 2014 articles reporting on work done at the Glomerular Disease Therapeutics Laboratory at the University of Alabama by Clement[16] and Chugh.[17] Clement reported that a prior study from their lab had demonstrated increased expression of angiopoietin-like 4 in podocytes in human and experimental minimal change disease. Pet. Ex. 34 at 1. In their study reported in *Nature Medicine*, Clement and his group demonstrated that angiopoietin-like 4 is an important biological mediator of nephrotic syndrome and is a critical link between proteinuria and hypertriglyceridemia. Id. at 9. Building from the Clement study, Chugh reported that "the central role played by [angiopoietin-like 4] in nephrotic syndrome (on par in importance with albumin, free fatty acids, and triglycerides) suggests that manipulating [angiopoietin-like 4] related pathways in the context of therapeutics has a high chance of success." Pet. Ex. 35 at 7.

Relating the theory to the present case, Dr. Kielstein noted that A.R. had a high fever, documented at 104.1 in the emergency room. Tr. at 83; Pet. Ex. 3 at 46. The fever suggested a cytokine response that likely could have been secondary to the vaccine. Id. at 84. He said that cytokine or inflammatory responses are known to cause alterations in angiopoietin-like 4, although the cytokines are not specifically measured in clinical practice. Id. at 83-84. Dr. Kielstein also explained that there may be a T-cell response to the hepatitis A antigen occurring in the five days intervening between the vaccine and the recognition of full blown nephrotic syndrome on November 4. See Tr. at 72-75. But when the court posed a question to him positing that a cytokine response to the vaccine caused the fever and asking whether it was likely that the innate response to the vaccine could cause the necessary injury in the kidney, Dr. Kielstein responded, "I don't know, because we are making the data, looking at that, and this is a very fascinating field." Id. at 84. He said that it is possible and cannot be ruled out that in the presence of an underlying genetic situation, the rapidly occurring innate response to a vaccine could be the causative agent in nephrotic syndrome involving the angiopoietin-like 4 pathway. Id. at 84.

Dr. Kielstein noted that Shalhoub had proposed the T-cell explanation for nephrotic syndrome over 30 years ago. Pet. Ex. 31 at 2 (citing Pet. Ex. 32[18]). Dr. Kaplan agreed that a systemic T-cell response is a hypothesis that has been in the literature, but he opined that it has been shown to have gaping holes in it during the intervening years. Tr. at 146-47. He opined that there are more elegant studies today and that the world has moved on from that hypothesis. Id. Dr. Kaplan, while discounting the continued vitality of the T-cell response, did express interest in the angiopoietin-like 4 theory, which he acknowledged had been introduced to him by Dr. Kielstein in this case. Tr. at 142-43. However, he argued that there is no literature linking vaccines or hepatitis A vaccines, in particular, to any dysfunction in angiopoietin-like 4. Id. at 144-45. Dr. Kaplan provided the historical perspective of the challenge that has been presented to his specialty of

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[16] Pet. Ex. 34, Lionel C. Clement et al., *Circulating Angiopoietin-Like 4 Links Proteinuria With Hypertriglyceridemia in Nephrotic Syndrome*, 20 NATURE MEDICINE 37 (2014).

[17] Pet. Ex. 35, Sumant S. Chugh, et al., *Angiopoietin-Like 4 Based Therapeutics for Proteinuria and Kidney Disease*, 5 FRONTIERS IN PHARMACOLOGY 23/1 (2014).

[18] Pet. Ex. 32, Robert J. Shalhoub, *Pathogenesis of Lipoid Nephrosis: A Disorder of T-Cell Function*, THE LANCET 556 (1974).

understanding the causal mechanism of this disease, a history with which Dr. Kielstein agreed. He asserted that in spite of the "hundreds of millions of vaccines" administered all over the world over the last 50 years, the prevalence of this kind of nephrotic syndrome has remained absolutely constant. Id. at 132. He opined that with all of the new vaccines administered someone would likely have noticed an upsurge in cases over this period of time. Id. Instead, there have only been three to five cases of nephrotic syndrome reported in the literature after vaccines of any kind. Id.

Dr. Kaplan stated that for him to be convinced that there was a causal link between a vaccine and minimal change nephrotic syndrome there would have to be quite a number of cases, a reasonable pattern, and a reasonable evolution and plausible scientific theory behind it. Tr. at 153. While Dr. Kaplan's standard of proof may demand something more than is required by this Program, the case does not fall on that testimony. The bigger problem is that there seems to be a genuine lack of understanding about the cause of this disease entity among nephrologists even though nephrotic syndrome has been studied for many years. Dr. Kaplan observed that in all of the case reports discussing the occurrence of nephrotic syndrome after vaccination, the authors say "we just don't know how this is happening. We have these possibilities, and yet we don't know what the actual cause is or what the sequence is." Id. A review of all of the articles submitted by the parties verifies that statement. See, e.g. Pet. Exs. 15-16[19]; See also Pet. Exs. 17-20, 27.[20]

Further, the T-cell theory does not appear to work in this case, as Dr. Kielstein acknowledged that the likely onset date of the minimal change syndrome in this child was within 36-40 hours of the vaccine, while admitting that our current understanding would suggest that it would take at least three or four days for a T-cell reaction to occur. Tr. at 73-75. This would seem to be particularly true when the reaction is to the first exposure to the antigen as it was in this case. Dr. Kielstein proposed that there may well be a combination of innate and adaptive immune responses involving the cytokines generated by the initial non-specific reaction to the vaccine impacting the angiopoietin-like 4, causing a loss of the "barbed wire on the fence," allowing the protein to spill into the urine. He seemed to propose that T-cells may be involved as well but it was not clear how or where in the sequence that may occur if the mechanism is a combined one. See, e.g. id. at 74, 77, 117; Pet. Ex. 31 at 2. While innate or inflammatory disruption of the angiopoietin-like 4 pathway may, at some point, prove to be a viable theory, at the present time it appears to be a bridge too far, too vague and too uncertain in terms of the triggering mechanism and sequence of the events in this case. In fact, the Clement study appeared to demonstrate that enhancement of

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[19] Pet. Ex. 15, Sila Ozdemir et al., *Nephrotic Syndrome Associated With Recombinant Hepatitis B Vaccination: A Causal Relationship or Just a Mere Association?*, 13 NEPHROLOGY DIALYSIS TRANSPLANTATION 1888, 1889 (1998) ("The pathophysiology of MCNS is still unknown"); Pet. Ex. 16, F. Macario et al., *Nephrotic Syndrome After Recombinant Hepatitis B Vaccine*, 43 CLINICAL NEPHROLOGY 349, 349 (1995) ("A causal relation cannot be easily established considering what is currently known about the pathophysiology of minimal change disease").

[20] Pet. Ex. 17, Ismail Islek et al., *Nephrotic Syndrome Following Hepatitis B Vaccination*, 14 PEDIATRIC NEPHROLOGY 89 (2000); Pet. Ex. 18, Y. Kikuchi et al., *Minimal Change Nephrotic Syndrome, Lymhpadenopathy and Hyperimmunoglobulinemia After Immunization with a Pneumococcal Vaccine*, 58 CLINICAL NEPHROLOGY 68 (2002); Pet. Ex. 19, J.T. Kielstein et al., *Minimal Change Nephrotic Syndrome in a 65-Year-Old Patient Following Influenza Vaccine*, 54 CLINICAL NEPHROLOGY 246 (2000); Pet. Ex. 20, Christian Clajus et al.. *Minimal Change Nephrotic Syndrome in an 82 Year Old Patient Following a Tetanus-Diphtheria-Poliomyelitis Vaccination*, 10:21 BMC NEPHROLOGY (2009); Pet. Ex. 27, M.J. Chamberlain et al., *Oliguric Renal Failure in the Nephrotic Syndrome*, 35 QJ MED 215 (1966).

angiopoietin-like 4 reduced existing proteinuria, but did not address how the angiopoietin-like 4 may have been altered in the podocytes in the first place, leading to the onset of the disease. See generally, Pet. Ex. 34.

Dr. Kielstein labored valiantly to propose a credible theory to explain this case, and may well have touched upon a theory that proves meritorious in the future, but he candidly acknowledged that there remains great mystery in the understanding of the causation of this disease. Without an understanding of the causation of the disease, it is not possible to come to a conclusion about vaccine causation or causation by a specific vaccine such as hepatitis A. Accordingly, though the timing in this case does appear powerful, based on the state of current medical knowledge, the underlying scientific theory is not sufficient to meet the requirements of Althen Prong I by a preponderance of the evidence. While I understand that this result will be disappointing to the Rus family, and empathize that A.R. has unfortunately suffered from this rare disease, I am unable to find that there is a causal link to the vaccine and compensation must be denied.

V. CONCLUSION

For all of the reasons discussed above, I find that petitioners have not established entitlement to compensation and their petition must be dismissed. In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, the clerk is directed to enter judgment consistent with this decision.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master