In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 05-306V
December 17, 2007
To be Published

MADISON DERIBEAUX, a minor, by her parents and natural guardians, GUS DERIBEAUX and KIMBERLY BURSHIEM,	*	
Petitioners,	*	
v.	*	Seizures one day after DPaT and HiB vaccinations with complications of Kawasaki disease, enterovirus, and immune deficiency
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Clifford J. Shoemaker, Vienna, VA, for petitioners.
Glenn A. MacLeod, Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioners filed a petition on March 11, 2005, under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that acellular DPT vaccine on March 28, 2002

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

caused Madison Deribeaux (hereinafter, "Madison") fever, reduced consciousness, seizures, and developmental delay. Madison was diagnosed with atypical Kawasaki disease.[2] The fever and seizures began within 24 hours of vaccination although her spiking fevers began approximately two weeks after the onset of her seizures when her temperature rose to 107.5º.

A hearing was held on September 20, 2007. Testifying for petitioners were Dr. Carlo Tornatore (a neurologist), Kimberly Burshiem (Madison's mother), and Dr. Joseph Bellanti (an immunologist). Testifying for respondent were Dr. Russell Snyder (a pediatric neurologist) and Dr. Brian Ward (an infectious disease specialist).

FACTS

Madison was born on August 19, 2001.

On Monday, October 8, 2001, Madison was brought to Baptist Hospital of Miami Emergency Department because of fever of 100.4º which had started several days before. Med. recs. at Ex. 2, p. 12. She was drinking less at night and her brother had been sick for one month. She was on Augmentin for sinusitis. *Id.* She had had bronchiolitis three weeks earlier. *Id.* She had a mild runny nose since the day before. She had vomited and had mucus in her stools. *Id.* She had had similar symptoms previously. *Id.* The clinical impression was fever and upper respiratory infection. Med. recs. at Ex. 2, p. 13. The nurses' notes reveal that Madison had

[2] Kawasaki disease is "a syndrome of unknown etiology, usually affecting infants and young children, associated with vasculitis of the large coronary vessels and numerous other systemic signs, including fever, conjunctival injection, changes of the oropharyngeal mucosa, cervical lymphadenopathy, and maculoerythematous skin eruption that becomes confluent and bright red in a glove-and-sock distribution; the skin becomes indurated and edematous and often desquamates from the fingers and toes." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 536.

vomited four times and her temperature began on Friday. Med. recs. at Ex. 2, p. 14. A blood culture was negative after five days of incubation. Med. recs. at Ex. 2, p. 39.

She received acellular DPT on Thursday, March 28, 2002.

On March 29, 2002, an EMS report states that it came to Madison's house where she was unconscious and had an axillary temperature of 100.3.º She had received her six-month immunizations, including DPT, the day before. Med. recs. at Ex. 5, p. 1.

On Friday, March 29, 2002, Madison was brought to Baptist Hospital Emergency Department having started tonic/clonic seizing 10 minutes earlier. She had a temperature of 98.1.º Med. recs. at Ex. 2, p. 89. She had upper airway congestion and a runny nose. Med. recs. at Ex. 2, p. 48. Her temperature at her initial assessment was 97º axillary. Med. recs. at Ex. 2, p. 114. She had previously been brought to Baptist Hospital in August 2001, but was not admitted. *Id.*

On Friday, March 29, 2002, Dr. Arcenio M. Chacon wrote an admission note that Madison was referred to him from the ER with a history of sudden onset of generalized tonic/clonic seizures with no fever. Med. recs. at Ex. 2, p. 97. She had a complete septic work-up in the ER which was negative. Her CT scan of the brain was negative. *Id.* On March 29, 2002, at 10:00 p.m., Madison had an axillary temperature of 99.8º. Med. recs. at Ex. 2, p. 158. At midnight, she had a temperature of 103.6º rectally. *Id.* At 7:00 a.m. on March 30th, Madison had a temperature of 100.7º rectally. *Id.*

On Saturday, March 30, 2002, Dr. Chacon and Dr. Alfonso wrote a Consultation Report stating that Madison was fine until 7:00 p.m. when she developed a generalized seizure which lasted about one hour. Afterward, she had multiple smaller seizures. She did not vomit or have

diarrhea. She had received DPaT on Thursday. She had had a runny nose on Friday and, after the seizure, a temperature of 103º. She did not have fever prior to her seizure. She was active and playful. Med. recs. at Ex. 2, p. 45. Her brother had had a febrile seizure at the age of 1 and ½ years. Med. recs. at Ex. 2, p. 97. The doctors suspected a viral syndrome. Med. recs. at Ex. 2, p. 45.

On March 30, 2002, Madison had temperatures of 99º (axillary) at 8:00 a.m., 100º (axillary) at 10:00 a.m., 98.6º rectally at noon, 100.6º rectally at 4:00 p.m., 98.9º (axillary) at 5:00 p.m., 102º rectally at 6:00 p.m., 97º (axillary) at 10:00 p.m., and 96.9º (axillary) at midnight. Med. recs. at Ex. 2, p. 160. On March 31, 2002, Madison had temperatures of 97.1º (axillary) at 2:00 a.m., 100.4º (axillary) at 4:00 a.m., and 99.9º (axillary) at 6:00 a.m. *Id.* On March 31, 2002, Madison had temperatures of 99º (axillary) at 7:10 a.m., 100.6º rectally at 4:00 p.m., and 102.1º rectally at 6:30 p.m. Med. recs. at Ex. 2, p. 166. On March 31, 2002, Madison had a temperature of 100.4º (axillary) at 4:00 a.m. and of 99.9º (axillary) at 6:00 a.m. Med. recs. at Ex. 2, p. 167. On March 31, 2002, Madison had temperatures of 98.9º (axillary) at 8:00 a.m. and 99º axillary at noon. Med. recs. at Ex. 2, p. 168, 174.

A fever chart at Baptist Hospital from March 31, 2002 to April 6, 2002 shows Madison had a temperature of 97.0º and 97.6º on March 31st; 98.6º, 97.6º, 96.6º, 96.5º, and 97.4º on April 1st; 97.4º, 98.9º, 97.5º, 98.7º, and 96.5º on April 2nd; 96.7º, 96.5º, 98.3º, 98.4º, and 96.4º on April 3rd ; 97.9º, 100º, 100.6º, 98.2º, 97.5º, and 97.2º on April 4th ; 97.7º, 96.4º, 97º, 97.1º, and 96.2º on April 5th ; 96.6º, 98.6º, 97º, 99.9º, and 97.4º on April 6th. Med. recs. at Ex. 2, pp. 202-03.

On April 5, 2002, a nurse's note says Madison was active, alert, and afebrile with some nasal congestion. Med. recs. at Ex. 2, p. 146. On April 7, 2002, Madison had temperatures of

96.5º at 8:00 a.m., 100.7º rectally at noon, 99.6º rectally at 4:00 p.m., and 100.7º rectally at 10:00 p.m. Med. recs. at Ex. 2, p. 184. On April 8, 2002, Madison had temperatures of 96.4º rectally at 2:00 a.m. and 97.5º rectally at 6:00 a.m. *Id.* She had temperatures of 97.8º at 10:00 a.m. and 97.6º at noon that same day. Med. recs. at Ex. 2, p. 192.

On April 8, 2002, Madison was discharged at 2:38 p.m. Med. recs. at Ex. 2, p. 198. Dr. Jeronimo J. Ramirez wrote the discharge summary. Med. recs. at Ex. 2, p. 95. Madison had been admitted to the PICU with atypical prolonged febrile seizure, lasting about 20 minutes. She had another episode of seizure on April 6, 2002, lasting 30 seconds related to a low-grade fever. She had upper airway congestion and viral syndrome. She was alert, active, and interacting well. She was discharged with a diagnosis of atypical prolonged febrile seizure. *Id.*

On April 9, 2002, Madison was readmitted to Baptist Hospital because she had a tonic-clonic generalized seizure lasting 10 minutes. She was febrile during the episode. Madison's mother said she had a low-grade temperature. Med. recs. at Ex. 2, p. 243. Dr. Antonia R. San Jorge did a consultation. Med. recs. at Ex. 2, p. 250. On April 5 and 6, 2002, Madison had a temperature spike to 101º with another seizure. On April 8, 2002, Madison did well for 12 hours and started once again to have fevers. In the early morning hours of April 9, 2002, she had a temperature spike to 101.5º and a generalized seizure, after which her temperature went up to 103.3.º Madison's two and ½ year-old brother has also had a fever for about 14 days. Madison's mother had been coughing and feeling ill for the prior two weeks. *Id.* Dr. San Jorge thought Madison might have a superimposed viral syndrome. Med. recs. at Ex. 2, p. 251. Madison's sibling had had one febrile seizure at the age of 18 months. Med. recs. at Ex. 2, p. 249.

On April 9, 2002, Madison's temperature was 103.5º at midnight. Med. recs. at Ex. 2, p. 318. On April 10, 2002, Madison's temperatures were 102º rectally at 3:15 a.m., 101.4º rectally at 8:10 a.m., 102.8º at 4:10 a.m., and 104.3º rectally at 10:30 a.m. Med. recs. at Ex. 2, pp. 310, 318.

On April 10, 2002, Dr. Chacon wrote a discharge/transfer summary that Madison's EEG was abnormal and she was placed on phenobarbital. Med. recs. at Ex. 2, p. 254. Madison's mother had a history of herpes. Madison was being transferred to Miami Children's Hospital. *Id.*

On April 10, 2002, Madison had a CT scan of her brain which showed no evidence of acute intracranial pathology but did show pansinus disease. Med. recs. at Ex. 4, p. 684.

On April 11, 2002, Madison had an EEG done which was normal. Med. recs. at Ex. 4, p. 1204.

On April 11, 2002, Madison had an EKG which showed mild pulmonary artery hypertension, small right pleural effusion, and qualitatively good left ventricular systolic function. Med. recs. at Ex. 4, pp. 1202-03.

On April 12, 2002, an MRI was done on Madison's brain with gadolinium and FLAIR. Med. recs. at Ex. 4, p. 687. She was normal without pathologic enhancement, but she did have inflammation involving the right ethmoid and both mastoid and middle ear cavities. *Id.*

On April 13, 2002, an esoteric test detected enterovirus RNA by RT-PCR (reverse transcription-polymerase chain reaction) in Madison's plasma, but not in her urine. Med. recs. at Ex. 4, p. 1026.

Also on April 13, 2002, Madison's IgG was low at 165 (normal ranges from 208-868). Ex. 4, p. 998. Her IgM was low at 23.9 (normal ranges from 32.0-120.0). Two days earlier, on April 11, 2002, her IgM was normal at 34.3. *Id.* On April 13, 2002, her IgE was low at 3.15 (normal ranges from 10.00-180.00). *Id.* Her C3 complement was low at 63 (normal ranges from 78-183). *Id.*

On April 16, 2002, Dr. Richard Schiff, an immunologist, examined Madison. Med. recs. at Ex. 4, p. 1040. She had been in excellent health until two weeks previously. One day after she received DPaT and HiB, she had a prolonged seizure lasting more than an hour associated with tonic clonic activity and duskiness. She was admitted to Baptist and had a temperature of 100.3º on admission which went up to 103.3º during the night. She was started on phenobarbital and treated with acyclovir and Rocephin. All cultures were negative. She was better within two days and discharged, seeming to be normal for five days. She had a second seizure lasting about five minutes which was tonic-clonic and associated with eyes rolling back. Temperature was 101.5º and she was sent home after one day but, the next morning, had another seizure on April 10, 2002, which was different. She turned blue and was unresponsive. She was treated with Ativan.

Around 5:00 p.m., she turned purple and her temperature rose to 107.5º whereupon she was transferred to the PICU. Cultures were still negative, including herpes PCR (polymerase chain reaction). MRI, EEG, and EKG were normal. On April 13, 2002, she seemed septic with low blood pressure and mottling. She was given one dose of IVIG at about 500 mg/kg. She improved somewhat. Cultures remained negative. Her neurological examination was non-focal. Dr. Schiff wrote, "The problem started one day after she received immunizations, so we need to consider that the seizures, at least are related. However, that would not explain the high fever to

over 107º F." *Id.* Madison's IgA was normal, indicating she did not have a primary immune deficiency. Med. recs. at Ex. 4, p. 1041. Her IgM was normal on April 12th and low on April 13th. That could be due to the variability of the test. Dr. Schiff recommended that the pediatrician submit a VAERs report for possible adverse vaccine reaction. *Id.*

On April 20, 2002, Madison was discharged on phenobarbital from Miami Children's Hospital. Med. recs. at Ex. 4, p. 680.

On May 15, 2002, Madison had an EKG done which showed no coronary abnormalities and qualitatively good left ventricular systolic function. Med. recs. at Ex. 4, p. 678.

On September 16, 2002, Madison went to Miami Children's Emergency Department with a seizure and a history of fever the day before. Med. recs. at Ex. 4, p. 661. She was convulsing in the ED. Her temperature was 102.6.º *Id.* She had a runny nose. Med. recs. at Ex. 4, p. 648. She had had 15 febrile seizures since the age of six months. She was diagnosed with atypical Kawasaki disease. *Id.* At 5:55 p.m., her rectal temperature was 104.2.º Med. recs. at Ex. 4, p. 644. She was diagnosed with a viral syndrome. Med. recs. at Ex. 4, p. 630.

On January 29, 2003, Madison went to Miami Children's Hospital Emergency Department with a history of three seizures that day and a rectal temperature of 104.4.º Med. recs. at Ex. 4, p. 531. She was transferred for admission. Med. recs. at Ex. 4, p. 594.

On January 30, 2003, a pathologic test of Madison's blood showed decreased T and B lymphocyte subsets. Med. recs. at Ex. 4, p. 622. Her CD19+ or B cells was 281 (normal ranges from 500-1500). Her CD4+/CD3+ or T-helper cells was 760 (normal ranges from1020-3600). Her CD8+/CD3+ or T cytotoxic cells was 211 (normal ranges from 570-2230). *Id.*

Also, on January 30, 2003, Madison had an EEG done which was normal. Med. recs. at Ex. 4, p. 624.

On February 1, 2003, Madison was discharged. Med. recs. at Ex. 4, p. 603.

On April 28, 2003, Madison went to Miami Children's Hospital Emergency Department. Med. recs. at Ex. 4, p. 470. She was admitted because she was manifesting a new seizure type. Med. recs. at Ex. 4, p. 481. Initially, she had several generalized tonic clonic seizures averaging one to two a week. Med. recs. at Ex. 4, p. 482. Most were associated with fever. She was developmentally normal. Recently, Madison experienced focal seizures involving only one side of the body. Her parents also noticed that she was exhibiting sudden jerky movements and blanked out with an upward gaze for a few seconds. *Id.* She had a history of three focal seizures, two of them left-sided. Med. recs. at Ex. 4, p. 394. She had a runny nose, cough, and a right ear ache. *Id.* Her temperature was 100.6º rectally. *Id.* The impression was epileptic seizure. Med. recs. at Ex. 4, p. 395.

On April 29, 2003, an esoteric test of Madison's serum did not detect enterovirus RNA by RT-PCR. Med. recs. at Ex. 4, p. 461.

On April 30, 2003, Madison had an abnormal brain MRI for the first time, showing delayed myelination. Med. recs. at Ex. 4, p. 397. She had abnormal signal intensity of the periventricular[3] white matter and white matter of the centrum semiovale.[4] *Id.*

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[3] Periventricular means "around a ventricle." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1408.

[4] Centrum semiovale means "semioval center: the white matter of the cerebral hemispheres which underlies the cerebral cortex and which, in horizontal sections superior to the corpus callosum, has a semioval shape; it contains projection, commissural, and association fibers." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 333.

On April 30, 2003, an esoteric test detected enterovirus RNA by RT-PCR (presumably in her serum), but did not detect it in her cerebrospinal fluid. Med. recs. at Ex. 4, p. 461.

On April 30, 2003, Madison had new seizures with left-sided twitching and left leg stiffness. She was afebrile. Med. recs. at Ex. 4, p. 499.

On April 30, 2003, an EEG showed excessive fast activity likely due to medication effect. Dr. Michael Duchowny and Dr. Sayed Naqvi opined it was a normal EEG in the sedated sleep state. Med. recs. at Ex. 4, p. 511.

On May 2, 2003, Madison was discharged from the hospital. Med. recs. at Ex. 4, p. 509.

On July 23, 2003, Madison was in Miami Children's Hospital. Med. recs. at Ex. 4, p. 358. Dr. Cutilla, an infectious disease specialist, wrote she possibly developed her problem after her third dose of acellular DPT. Madison had had fevers since March 2002. From March to May, she had a daily temperatures of 100-102.º In June and July, she had temperatures from 100 to 100.5.º Fevers had improved but were persistent. She had daily seizures since April. On April 28, 2003, her cerebrospinal fluid was negative. On May 2, 2003, her cerebrospinal fluid was negative. *Id.*

On July 23, 2003, Madison had an EKG done which showed no significant coronary artery ectasia (dilatation) or aneurysmal formation. She had qualitatively good left ventricular systolic function. Med. recs. at Ex. 4, p. 374.

On July 29, 2003, Madison had an EKG done which showed a small restrictive arterial duct and qualitatively good left ventricular systolic function. Med. recs. at Ex. 4, p. 372.

On August 28, 2003, an esoteric test detected enterovirus RNA by RT-PCR in Madison's whole blood. Med. recs. at Ex. 4, p. 350.

On September 16, 2003, Madison was brought to Miami Children's Hospital with hypogammaglobulinemic seizures. Med. recs. at Ex. 4, p. 336.

On October 21, 2003, Madison was brought to Miami Children's Hospital Emergency Department after having had a seizure in a pool, lasting about 10 seconds. Med. recs. at Ex. 4, p. 324. Her temperature was 98.5.º *Id.* Her past history included chronic enterovirus infection. Med. recs. at Ex. 4, pp. 325, 327. She was noted to have frequent viral infections and fever. Med. recs. at Ex. 4, p. 327.

On November 7, 2003, Madison went to Miami Children's Hospital. Med. recs. at Ex. 4, p. 300.

On November 7, 2003, Madison had a brain MRI. Comparing it with the prior brain MRI of April 30, 2003, Dr. Santiago Medina saw further progression of myelination. However, there was increased T2-weighted signal in the periventricular white matter that was more marked posteriorly. Differential diagnosis included gliosis[5] versus hypomyelination. Med. recs. at Ex. 4, p. 304.

On November 7, 2003, Madison had MR spectroscopy of the left posterior periventricular white matter. Med. recs. at Ex. 4, p. 303. She had mild elevation of the myoinositol peak in the left posterior periventricular white matter most likely related to underlying gliosis and less likely hypomyelination. *Id.*

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[5] Gliosis is "an excess of astroglia in damaged areas of the central nervous system; see also *astrocytosis*." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 778. Astroglia are "astrocytes." *Id.* at 170. Astrocytosis is "the proliferation of astrocytes owing to the destruction of nearby neurons during a hypoxic or hypoglycemic episode." *Id.* at 170.

On November 9, 2003, Madison had a seizure. She was discharged from the hospital on November 10, 2003 with a diagnosis of hypogammaglobulinemia with recurrent infections. Med. recs. at Ex. 4, p. 299. She was receiving intravenous immunoglobulin (IVIG). Med. recs. at Ex. 4, p. 298.

On December 1, 2003, Madison went to Miami Children's Hospital. Med. recs. at Ex. 4, p. 291. Madison had a temperature of 101.3º axillary two days earlier which was two days past her last IVIG infusion. Med. recs. at Ex. 4, p. 293.

On December 27, 2003, Madison went to Miami Children's Hospital with a temperature of 101º and 13 seizures that day. Med. recs. at Ex. 4, p. 264.

On December 27, 2003, Dr. Jose Carro, an immunologist, wrote that Madison had delayed immunizations secondary to seizures with vaccine-induced fever. Med. recs. at Ex. 4, p. 261. Dr. Carro felt that Madison was immunocompromised but not so severely that she required more intense immune support. Unless she deteriorated clinically or cultures revealed new information, Dr. Carro would not administer IVIG at that time until her next scheduled infusion. *Id.*

On December 27, 2003, an infectious disease specialist wrote that after Madison received her last IVIG seven days earlier, she had been having fevers up to 103º as well as an increase in seizures. Med. recs. at Ex. 4, p. 260.

On December 27, 2003, a doctor whose name may be S. Tamaken wrote that, on the day before, Madison had fevers up to 104º twice and 15 seizures, some lasting one minute, some consisting only of a cry and lasting a few seconds. Med. recs. at Ex. 4, p. 258. She had a chronic enterovirus infection in her serum. *Id.*

On December 28, 2003, Madison was noted to be clinically improved, less febrile and with no seizures. Med. recs. at Ex. 4, p. 276. She was discharged home. Med. recs. at Ex. 4, p. 270.

On January 9, 2004, Dr. Carro wrote that two days after Madison's last infusion, she had high fever and then six seizures and was admitted to the hospital. She still had fevers every day. Her enterovirus infection had cleared. Med. recs. at Ex. 4, p. 208.

On February 20, 2004, another doctor noted that Madison's seizure medications were increased. She was having daily fevers. Med. recs. at Ex. 4, p. 198.

On March 28, 2004, Madison was brought to Miami Children's Hospital Emergency Services because she had a seizure while in a kiddy pool and went face first in the water for two to three seconds. Med. recs. at Ex. 4, p. 187.

On April 13, 2004, Madison was brought to Miami Children's Hospital Rehabilitative Services. She was pinching, biting, hitting herself, banging her head, licking people and things, had abnormal gait, was impulsive, and showed no fear. Med. recs. at Ex. 4, p. 168. Madison was diagnosed with ataxia and fine motor delay. Med. recs. at Ex. 4, p. 163. She functioned low in all areas of sensory integration and attention span. *Id.*

On June 3, 2004, Madison underwent a Video-EEG. Med. recs. at Ex. 4, pp. 152-53. Madison had a history of generalized tonic-clonic seizures since eight months of age, but now presented with a new seizure type, characterized by left hemibody tonic-clonic activity and episodes of right hemibody tonic-clonic activity. Med. recs. at Ex. 4, p. 152. She had an abnormal Video-EEG study due to the presence of an admixture of theta and delta slowing seen diffusely in both hemispheres. These findings indicated diffuse cerebral dysfunction without

evidence of lowered seizure threshold. There was one clinical event characterized by brief myoclonic activity with diffuse onset electrographically. Med. recs. at Ex. 4, p. 153.

On June 22, 2004, Madison went to Miami Children's Hospital Emergency Department after hitting her head while having a seizure. Med. recs. at Ex. 4, p. 140. She underwent a brain CT scan which showed a subgleal hematoma in the occipital region. Her ventricles were at the upper limits of normal. There was no extra axial fluid collection. She had mucosal thickening of the paranasal sinuses. Med. recs. at Ex. 4, p. 150.

On October 22, 2004, Madison was noted to be having seizures only at night. Med. recs. at Ex. 4, p. 122.

On November 15, 2004, Madison had a brain MRI, which was compared with the brain MRI of November 7, 2003. Med. recs. at Ex. 4, p. 113. When compared to the MRI of a year before, Madison had further myelinization of her brain. However, there was incomplete myelinization of the subcortical white matter in the frontal region as well as the temporal lobes anteriorly. The ventricles were normal in size and shape. There was no deep gray matter signal abnormality. There was persistent periatrial posterior centrum semiovale white matter signal intensity which was symmetrical and might represent areas of slow myelinization. There was no extra-axial fluid collection. There was loss of the internal architecture of the left hippocampus with minimal high signal intensity. *Id.*

On February 8, 2005, Madison was in Miami Children's Hospital. Med. recs. at Ex. 4, p. 64. She had three types of seizure: tonic-clonic (one per day), myoclonic (one per day), and focal (last seen three weeks before). *Id.* During the last six months, her seizures had been at night. Her mother said that Madison stopped progressing after she was one year of age. *Id.* Her

enterovirus infection lasted one year. She was cleared by Dr. Lauffer six months ago. She received IVIG every three weeks for her immunodeficiency in IgG 2 and IgG 4. *Id.* Madison was begun on a ketogenic diet. Med. recs. at Ex. 4, p. 55.

On February 22, 2005, Dr. Carro noted that Madison was on a ketogenic diet. She still got temperatures from 99-101º and was still having seizures: four grand mal and 20 myoclonic in the last two weeks. She seemed however more alert. Med. recs. at Ex. 4, p. 95.

On March 30, 2005, Madison had an EKG which was normal. Med. recs. at Ex. 4, p. 88.

On April 1, 2005, Dr. Carro noted that Madison was still on a ketogenic diet and still having seizures but was felt to be cognitively improved. Med. recs. at Ex. 4, p. 86.

Other Submitted Material

Petitioners filed Ex. 7, p. 15, an article entitled "Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids," by L.A. Jackson, et al., 21 *Ped Infect Dis J* 781-85 (2002). The authors studied children who received DPaT, which is less reactogenic than whole-cell DPT, and found a rate of seizures within two days of DPaT vaccination among children younger than two years of age to be 1 per 19,496 vaccinations. *Id.* at 784. In trying to ascertain why reactions to acellular DPT occur, the authors posited a cell-mediated immune response to vaccine antigens as a possibility. *Id.* at 785.

Petitioners filed Ex. 7, p. 21, an article entitled "Kawasaki Disease: A Maturational Defect in Immune Responsiveness," by T.W. Kuijpers, et al., 180 *J Infectious Dis* 1869-77 (1999). The authors state:

> Kawasaki disease (KD) is an acute illness of early childhood characterized by persistent fever, induration and erythema of hands and feet, polymorphous rash, inflammation of the mucous membranes, bilateral conjunctivitis, and (cervical) lymphadenopathy.

Id. at 1869.

The authors posit a subtle immune defect in KD as an explanation for why so many different antigens, mostly of infectious origin, have been reported to precipitate KD. Extensive antigenic stimulation on top of an imbalanced immune system could explain the disease onset. *Id.* at 1876.

Petitioners filed Ex. 7, p. 31, a case report entitled "Kawasaki disease in an infant following immunisation with hepatitis B vaccine, " by D. Miron, et al., 22 *Clin Rheumatol* 461-63 (2003). The authors state that the association of hepatitis B infection and vasculitis has been extensively documented. In this case report, a 35-day-old infant developed fever one day after receiving his second hepatitis B vaccination. *Id.* at 461.He was diagnosed with Kawasaki disease based on prolonged fever, rash, conjunctivitis, mucous membrane erythema, edema of the extremities, increased level of acute-phase reactants, and echocardiographic dilation of the coronary artery. *Id.* at 462. The authors felt the strong temporal association should alert people to the possibility of Kawasaki disease as a rare side effect of hepatitis B vaccination. *Id.* at 463.

Petitioners filed P. Ex. 9, an article entitled "Clinical Features of atypical Kawasaki disease," by Y-C Hsieh, et al., 35 *J Microbiol Immunol Infect* 57-60 (2002). The authors stated that Kawasaki disease is a systemic vasculitis syndrome presumed to result from immunoregulatory abnormalities caused by infectious agents in immunologically susceptible people. *Id.* at 57.

Respondent filed Ex. C, which includes a number of articles, the first of which is entitled "Kawasaki Disease With Predominant Central Nervous System Involvement," by B. Tabarki, et al., 25 *Ped Neur* 239-41 (2001). (Respondent also filed this article as Ex. JJ.) The authors state:

> Kawasaki disease is an acute vasculitis of unknown etiology with varied clinical manifestations. Central nervous system involvement occurs in 0.4% of children with this disease and include seizures, ataxia, cerebral infarction, and subdural effusion.

Id. at 239.

They present the case of a four-year-old girl who had a two-day history of fever and anorexia, and a one-day history of progressive deterioration of consciousness with two focal seizures of less than five minutes. *Id.* Twelve months after onset, the girl's brain MRI showed diffuse and severe cerebral atrophy, characterized by enlargement of sulci[6] and ventricular dilatation. *Id.* at 240. They note that acute encephalopathy associated with Kawasaki disease has been reported in only a few children. *Id.* In one large series of 540 patients with Kawasaki disease, there were only two infants out of 540 who had central nervous system involvement. *Id.* The authors of this article reviewed literature discussing eight patients with acute encephalopathy associated with Kawasaki disease including two patients who had status epilepticus. *Id.* They theorize that since Kawasaki disease is a systemic vasculitis, there may be focal impairment of blood flow caused by cerebral vasculitis. *Id.* at 241. They also note that the most important complication of Kawasaki disease is cardiac involvement. *Id.*

The second article in respondent's Ex. C is "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease," by J.W. Newburger, et al., 110 *Circulation* 2747-71 (2004).

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[6] Sulci are "the furrows on the surface of the brain between the cerebral gyri." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1786.

The authors state, "Kawasaki disease is an acute, self-limited vasculitis ... characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy."[7] *Id.* at 2747. They also stated that coronary artery aneurysm or ectasia (dilatation) occurs in 15-25% of untreated children with the disease which may lead to myocardial infarction, sudden death, or ischemic heart disease. *Id.* at 2747-48. In the United States, Kawasaki disease is the leading cause of acquired heart disease in children. *Id.* at 2748. They state two hypotheses for the cause of Kawasaki disease: (1) a bacterial superantigenic toxin (polyclonal immune response), or (2) a conventional antigen (oligoclonal immune response) in which immunoglobulin A (IgA) plasma cells play a central role. *Id.* at 2749. They also state that Kawasaki disease may be an immunologic response to any of several different microbial agents although this has never been proved. *Id.* The authors continue:

> Striking immune perturbations occur in acute Kawasaki disease, including marked cytokine cascade stimulation and endothelial cell activation. The key steps leading to coronary arteritis are still being clarified, but endothelial cell activation, CD68+ monocyte/macrophages, CD8+ (cytotoxic) lymphocytes, and oligoclonal IgA plasma cells appear to be involved. The prominence of IgA plasma cells in the respiratory tract, which is similar to findings in fatal viral respiratory infections, suggests a respiratory portal of entry of an etiologic agent or agents.

Id. at 2749-50.

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[7] Lymphadenopathy is "disease of the lymph nodes." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1074.

Under " Table 1. Clinical and Laboratory Features of Kawasaki Disease," the authors list "Central nervous system" and include symptoms of extreme irritability, aseptic meningitis, and sensorineural hearing loss. *Id.* at 2751.

Respondent filed a final article under Ex. C which is a brief report entitled "Lateral Rectus Palsy in Kawasaki Disease," by B.J. Wurzburger and J.R. Avner, 18 *Ped Infect Dis J* 11:1029-31 (1999). The authors state that the reported rate of neurologic complications in Kawasaki disease, including facial nerve palsy, seizures, ataxia, encephalitis, hemiplegia and cerebral infarct is 1.1%. *Id.* at 1030. The patient who is the focus of the brief report had a transient sixth cranial nerve palsy. She complained of frontal headache, neck pain, and diplopia. She had no other findings on neurologic exam. *Id.* The authors conclude this was most likely a vasculopathic phenomenon secondary to Kawasaki disease that resolved spontaneously. *Id.*

Respondent filed Ex. H, a case study entitled "Bilateral subdural collections - an unusual feature of possible Kawasaki disease," by N.M. Bailie, et al., 5 *European J of Paediatric Neur* 79-81 (2001). The authors studied the case of a six-month-old boy who developed a non-specific persistent febrile illness three weeks before presentation. He became increasingly lethargic and had a prolonged right-sided seizure. A brain CT scan on day two of admission showed bilateral asymmetrical subdural[8] collections. Cranial MRI on day eight of admission showed enlargement of the subdural collections and a rim of enhancement around the left collection. *Id.* at 79. The

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[8] Subdural means "between the dura mater and the arachnoid." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1778. The dura mater is "the outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord...." *Id.* at 570. The dura mater of the brain is "composed of two mostly fused layers: an endosteal outer layer (endocranium) adherent to the inner aspect of the cranial bones... and an inner meningeal layer." *Id.* The arachnoid resembles a spider's web. *Id.* at 122.

baby responded well to IVIG and high-dose aspirin, subsequently repeated after a recurrence of fever. At two years, the child was well and normal. A brain CT scan at six months post-presentation showed complete resolution of the subdural collections. *Id.* at 80.

The authors note that subdural collections are rarely seen in classic Kawasaki disease which is "a multisystem disorder characterized by vasculitis of small and medium sized arteries." *Id.* at 80-81. "Neurological complications occur in 1.1-3.7% of children." *Id.* at 81. Extra-cerebral fluid collection in six children has been reported and due to vasculitis of dural vessels, although the neurologic outcome of those children was normal except for mild hearing impairment in one child. *Id.*

Respondent filed Ex. J, an article entitled "Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS)," by M.M. Braun, et al., 106 *Ped* 4:e51(1-7) (2006). Fever was the second most commonly reported event (25.0%) after DPaT vaccination. *Id.* at 3. Seizures occurred among 10.5% of DPaT vaccinees. *Id.* at 4 (Table 3).

Respondent filed Ex. K, an article entitled "Epidemiological Features of Kawasaki Disease in Taiwan, 1996-2002," by L-Y Chang, et al., 114 *Ped* 6:e678-e682 (2004). The authors describe Kawasaki disease as "an acute systemic febrile illness of unknown cause" which is "now the most common cause of acquired heart disease in children" and is "usually self-limiting." *Id.* at e678. The authors found the highest incidence of Kawasaki disease among children aged six months to one year, who had little maternal antibody, and who were generally more susceptible to infections, suggesting to the authors that infection may cause Kawasaki disease. *Id.* at e681. The authors state:

> In fact, some scientists have examined the evidence supporting the concept that KD is caused by infectious agents. Various infectious agents, including bacterial, viral, chlamydial, and rickettsial organisms, have been implicated as potential causes, as have certain immunologic agents such as bacterial toxin-mediated superantigens.

Id.

The incidence of Kawasaki disease is more common among Asians, but different among Asian countries, with Japan having the highest number, Taiwan second, Hong Kong third, and China fourth. *Id.* at e681-e682. These incidences were higher than those reported for Western countries such as the United States and the United Kingdom. The authors thought the difference in incidence could be due "to genetic and environmental factors or infectious factors." *Id.* at e682.

Respondent filed Ex. N, an article entitled "Kawasaki disease," by F. Falcini, 18 *Current Opinion in Rheum* 33-38 (2006). Dr. Falcini states that Kawasaki disease occurs mainly in Asian populations, mostly Japanese. However, in Hawaii, where most people are of Asian ancestry, the incidence is lower than in Japan, "supporting the assumption that both genetic predisposition and environmental factors are important." *Id.* at 33. A novel human coronavirus, "New Haven coronavirus" (NCo-NH), was identified in respiratory secretions of a six-month-old child with typical Kawasaki disease. A study of specimens of respiratory secretions of 11 Kawasaki disease children showed that eight (72.7%) tested positive for HCoV-NH by reverse-transcriptase polymerase chain reaction (RT PCR) in contrast to one (4.5%) out of 22 control patients. *Id.* at 34. Babies prone to allergies might be susceptible to Kawasaki disease because, in several

Japanese regions, pollen-related symptoms in children significantly increased over time as did the number of children with Kawasaki disease. *Id.*

Respondent filed Ex. S, an article entitled "Association of Nonpolio Enteroviral Infection in the Central Nervous System of Children With Febrile Seizures," by M. Hosoya, et al., 107 *Ped* 1:e12 (1-5) (2001). Out of 18 patients with simple febrile seizures, five had positive results of enteroviral genome in their cerebrospinal fluid as determined by enteroviral polymerase chain reaction (PCR). *Id.* at 1. The causative agent of febrile seizures in summer is attributed primarily to enteroviruses. *Id.* at 5. Enteroviruses, especially coxsackieviruses group A, often infiltrated into the central nervous system of patients with febrile seizures. *Id.*

Respondent filed Ex. U, an article entitled "Fever after Immunization: Current Concepts and Improved Future Scientific Understanding," by K.S. Kohl, et al., 39 *Clin Infectious Dis* 389-94 (2004). The authors state that fever can be as frequent as 30% to less than 70% among vaccinees receiving multiple vaccines or whole-cell DPT. *Id.* at 391.

Respondent filed Ex. CC, an article entitled "Superantigens, conventional antigens and the etiology of Kawasaki syndrome," by H.C. Meissner and D.Y.M. Leung, 19 *Ped Infect Dis J* 2:91-94 (2000). The authors state, "A number of epidemiologic and clinical observations suggest that Kawasaki syndrome is caused by an infectious agent." *Id.* at 91. They theorize that "it may be that infection leads to an immune-mediated syndrome only in an immunologically susceptible host." *Id.* However, "no microbe has been consistently associated with this syndrome"despite more than 25 years of study. *Id.* In contrast, "investigation into the immune status of children with Kawasaki syndrome has consistently revealed a profound degree of immunoregulatory abnormalities that are not characteristic of most other febrile exanthems of childhood." *Id.* The

authors focus on superantigens in bacterial and viral protein toxins because of the unusual degree of immune activation in patients with Kawasaki syndrome. Superantigens cause the release of an unusually large amount of cytokines from activated T cells. Cytokines mediate the disease process. *Id.* There are up to 20 known superantigens from bacteria and viruses. *Id.* at 93. The authors theorize:

> The following hypothesis has been proposed to explain the pathogenesis of this fascinating illness: a genetically susceptible host becomes colonized on the mucous membranes of the gastrointestinal tract by an organism that produces a toxin that behaves as a superantigen. ... Toxin is absorbed through the inflamed mucosal surface and stimulates local or circulating mononuclear cells to produce proinflammatory cytokines which in turn result in fever and the clinical picture of Kawasaki syndrome. In response to cytokine-induced stimulation, antigens are expressed on the surface of vascular endothelial, rendering them susceptible to attack by cytotoxic antibodies and activated T cells. Neoantigens on endothelial cells render the vessels more thrombogenic.

Id.

The authors theorize "that both superantigen-activated T cells and clonally related autoreactive T and B cells are necessary to produce the auoimmune vasculitis of Kawasaki syndrome. Both cell types participate in the immune-mediated disease process." *Id.* Thus, "a population of T cells, initially stimulated by a superantigen, are activated by a conventional antigen or autoantigen after they invade the coronary arteries." *Id.* at 93-94. Kawasaki syndrome has replaced rheumatic fever as the most common cause of acquired heart disease in children. *Id.* at 94.

Respondent filed Ex. GG, a short report entitled "Low incidence of febrile convulsion during the acute phase of Kawasaki disease in Japan," by H. Nozaki, et al., 164 *Eur J Ped* 650

(2005). The authors reviewed 217 Kawasaki disease patients in Japan from 1994 to 2004 and found only one girl who had a febrile convulsion among the 217. They calculated the incidence of febrile convulsion among patients with Kawasaki disease as 0.46% (1/217). *Id.* The authors studied three other papers on the same issue which reviewed 155, 540, and 177 patients respectively and the authors found only one patient with a febrile convulsion among them. On meta-analysis, they calculated the incidence of febrile convulsion in Kawasaki patients as 0.18% (2/1089) with a confidence interval of 0.02%-0.66%. The authors found the incidence of febrile convulsion among Kawasaki disease patients to be unexpectedly low. *Id.*

Respondent filed Ex. KK, an article entitled "Meningoencephalitis in Kawasaki disease," by K. Takagi, et al., 22 *No To Hattatsu* 5:429-35 (1990). The authors describe five Kawasaki disease patients with meningoencephalitis. CT scan revealed fluid collection in the frontal extracerebral space. They considered that meningoencephalitis in Kawasaki disease might develop in more severe cases with prolonged inflammatory changes. The reason is that Kawasaki disease involves "vasculitis of small arteries, arterioles, capillaries, and venules," consisting "of infiltration of lymphocytes and large mononuclear cells, and edema." *Id.* at R's p. 1 (article in Japanese). Four of the five patients had no neurologic sequelae. One patient had hearing difficulty three years after onset. *Id.* The authors thus considered the prognosis of meningoencephalitis in Kawasaki disease to be generally favorable. *Id.*

Respondent filed Ex. MM, an article entitled "White matter damage in neonatal enterovirus meningoencephalitis," by M.A. Verboon-Maciolek, et al., 66 *Neur* 1267-69 (2006). The authors discuss six neonates who had meningoencephalitis from enterovirus, five of whom presented with prolonged seizures and one of whom presented with systemic enteroviral disease.

MRI confirmed mild to severe white matter damage in all six children: two developed cerebral palsy; one was neurologically suspect; and three were developmentally normal. *Id.* at 1267. Enterovirus was cultured either from cerebrospinal fluid or the nasopharynx, or identified by PCR (polymerase chain reaction). *Id.* at 1267-68. The signal intensity in the white matter on MRI suggested petechial hemorrhages. *Id.* at 1268. A rash on clinical examination and occurrence in summer were clues to enterovirus infection. *Id.* at 1269. Three children with abnormal neurodevelopment were born preterm. *Id.*

Respondent filed Ex. NN, an article entitled "Kawasaki Disease. Infection, Immunity and Genetics," by C-L Wang, et al., 24 *Ped Infect Dis J* 11:998-1004 (2005). The authors state that in some countries where newborns receive Calmette-Guérin bacillus (BCG) vaccine, Kawasaki disease can be associated with erythematous induration or even ulceration of BCG scars in one-third of cases. *Id.* at 998. Erythema of the palms and soles occurs. *Id.* at 999. The pathology of necrotizing vasculitis of Kawasaki disease "suggests a primary role for monocytes-macrophages and T lymphocytes in the acute vascular injury observed." *Id.*

Respondent filed Ex. WW, an article entitled "Febrile convulsion during the acute phase of Kawasaki disease," by H. Yoshikawa and T. Abe, 46 *Ped International* 31-32 (2004). The authors studied 177 patients with Kawaski disease to determine how many had febrile convulsions during the course of their disease. None did. The authors state, "Febrile seizures in Kawasaki disease are considered to be extremely rare." *Id.* at 31.

Eight of the 177 patients had simple febrile convulsions during febrile illness except when they had Kawasaki disease. Two patients in the acute phase of Kawasaki disease had generalized convulsions associated with prolonged unconsciousness and pleocytosis in their

cerebrospinal fluid. *Id.* This was in the context of hyponatremia (too little salt). *Id.* at 32. In other studies of Kawasaki disease, febrile convulsions occurred in 1 out of 155, 8 out of 498, 1 out of 402, none out of 152, and none out of 540 cases respectively. *Id.*

TESTIMONY

Dr. Carlo Tornatore testified first for petitioners. Tr. at 11. He is associate professor of neurology at Georgetown University. Tr. at 13. His predominant interest is autoimmune disorders. He is the director of the multiple sclerosis and autoimmune disorders clinics. The majority of those patients have multiple sclerosis, but there is a group of patients with vasculitis. *Id.* Vasculitis affects the blood vessels of the brain and his patients have central nervous system vasculitis. In 80% of those cases, the cause is unknown. Tr. at 14.

In Dr. Tornatore's opinion, Madison had some immune deficiencies prior to her vaccination. Tr. at 15. On April 13, 2002 (P. Ex. 4, p. 998), Madison had an IgG level of 165, which is very low. The lower limit of normal is 208. Also, her IgM was low at 23.9. The lower limit of normal of IgM is 32. Two days before, it had been in the normal range (34.3) and then dropped. Madison's IgE level was very low at 3.15. The lower limit of normal is 10. Her C3 complement level was low at 64. The lower limit of normal is 78. Tr. at 16. These results indicate Madison had low antibody levels crossing three subtypes: IgM, IgE, and IgG. That means the humoral arm of her immune system was impaired. *Id.* This was within a week of vaccination.[9] Tr. at 17.

[9] Actually, this first test of Madison's immune system was two weeks after her acellular DPT and HiB vaccinations.

The cellular side of Madison's immune system tested on January 30, 2003 (P. Ex. 4, p. 622) showed a CD4 level (the T-helper) of 760. The lower limit of normal is 1,020. Madison's CD8 level (cytotoxic T-cells) was 211. The lower limit of normal is 570. *Id.* Madison had both humoral and cellular immune problems. The reason for her humoral problems might be the cellular problems. CD4 cells help regulate the B-cell function. If they are not working properly, the individual may not make adequate antibodies or may make weak antibodies in a dysregulated way. Tr. at 18. Although this second testing was performed eight months post-vaccination,[10] it still shows a persistent problem. *Id.*

After Madison received her vaccinations on March 28, 2002, she had febrile seizures with status epilepticus the day after. Tr. at 19. She required quite a number of different medications to stop the seizures. Madison's temperature at 10:00 p.m. was 99.8º but, at midnight, her temperature rose to 103.6º rectally. *Id.* Madison was very irritable during this period. Tr. at 20. Her temperature decreased to 100.7º rectally at 2:00 a.m. *Id.* Madison was crying. Finally, at 4:00 a.m., Madison slept, and, at 6:00 a.m., she was sleeping and afebrile after she had received Tylenol and Advil. *Id.* Dr. Tornatore agreed that Madison did not have a Table encephalopathy because she did not have 24 hours of significantly decreased level of consciousness. Tr. at 21, 25.

On March 30, 2002, at 7:10 a.m., Madison was very irritable and crying. *Id.* She was administered Tylenol rectally. At 8:50 a.m., she was febrile and irritable. Tr. at 22. Motrin was given. At 11:00 a.m., Madison was sleepy. She was given a sponge bath. At 8:00 p.m., she was irritable. *Id.*

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[10] Actually, this second immune test was 10 months post-vaccination.

Madison went on to have a chronic seizure disorder and now has 20 to 30 seizures per day (epilepsy) despite medication and is developmentally delayed. Tr. at 25-26. Dr. Tornatore connected Madison's first seizure after the acellular DPT with her subsequent seizures. Tr. at 26. Madison had an acute reaction to the vaccine with seizures, fever, and irritability. There are significant numbers of children who receive acellular DPT and have seizures. *Id.* Respondent's Exhibit J discusses infant acellular DPT immunization over two years as reported to VAERS. Tr. at 27. There were 63 serious reactions reported and 367 deaths. *Id.* Ninety-six convulsions were reported, which was 10 percent. Tr. at 28. Twenty-five percent of vaccinees had fever, while 25.7 percent had agitation. Tr. at 28-29.

Even though the amount of endotoxin in acellular DPT is less than it was in whole-cell DPT, there is still endotoxin in the acellular vaccine and most people recognize that the endotoxin component probably led to the neurologic issues with whole-cell DPT. Tr. at 31. There is much lot-to-lot variability in the amount of endotoxin. *Id.* Here, Madison had some prior immune deficiency. After the vaccination, she had associated fever and irritability, suggesting something diffuse occurred in her nervous system. Tr. at 32.

Madison also received HiB vaccine when she received acellular DPT vaccine and, according to Ex. J, Table 3, those who received HiB with DPT had more reactions.[11] *Id.* Madison's first seizure was caused by the toxicity of endotoxin on her nervous system, but she subsequently developed Kawasaki vasculitis, which can affect blood vessels. Her subsequent MRI showed very diffuse hypomyelination. Tr. at 34. Her brain MRI showed diffuse changes in

[11] However, DPTH included whole-cell DPT, not acellular DPT, and whole-cell DPT has more reactivity than acellular DPT. R. Ex. J, p. 1, of the text.

her white matter so Madison now has central nervous system involvement which could be the result of the Kawasaki vascular process. Tr. at 34-35.

Even if Madison had not developed Kawasaki disease, her initial seizure from the vaccination would have led to a chronic seizure disorder. Tr. at 35. After the initial toxic event, there was a seizure focus in her brain where the nerves have been injured, causing recurrent seizures. *Id.* All someone needs is one insult to the brain to cause chronic injury. Tr. at 35-36.

After Madison was discharged from Baptist Hospital, she returned with a second seizure and was transferred to Children's Hospital because of her repetitive seizures. At Miami Children's Hospital, she developed a rash around April 11, 2002. The first indication she had developed Kawasaki would date from that time. Tr. at 36. Dr. Tornatore's opinion is that Madison's reaction to acellular DPT caused her Kawasaki disease. *Id.* After she received the endotoxin, she developed fever and an immune problem. Perhaps her seizures were due to an early vasculitis since vasculitis can cause seizures. That may be how the Kawasaki initially presented. *Id.* But in classical Kawasaki, the rash occurs first. In petitioners' Ex. 7, p. 21, the Dutch article discussing Kawasaki disease, the authors state they could identify problems with these children's humoral immune system, i.e., their CD4 cells were not as active as they should have been. *Id.* Kawasaki is an autoimmune disease. *Id.* When confronted with an antigen, an immune system that is deficient has difficulty clearing it properly, leading to vasculitis. Tr. at 37-38. An infection might precipitate Kawasaki disease. Tr. at 39. Madison was exposed to bacterial antigens in acellular DPT, which her immune system could not clear properly and, 10 days later, she developed an immune response demonstrated as a rash. The timing between the vaccination and her subsequent development of Kawasaki makes immunologic sense. Tr. at 40.

Dr. Tornatore stated that the acellular DPT caused Madison's initial convulsion and chronic seizure disorder as well as Kawasaki disease. Tr. at 40-41. Because Madison's immune system is deficient, she had an abnormal response to the antigens in the acellular DPT and had a more prolonged fever. Tr. at 42. Dr. Tornatore denied that Madison had enterovirus in a rapid PCR test until a year after her vaccination.[12] Tr. at 43. Madison's abnormal brain MRI a year after vaccination could be from a combination of the Kawasaki and the seizure disorder. Tr. at 46. Her nervous system was injured, manifesting in seizure disorder and developmental delay. Tr. at 50.

In answer to the undersigned's question whether the vaccine was a substantial factor in causing Madison's first seizure even if Kawasaki disease were coincidentally about to become clinical, Dr. Tornatore answered yes because the acellular DPT added something very volatile into the immunologic mix at that point. Tr. at 55. Dr. Tornatore thought that Kawasaki was the more likely cause of the chronic seizure disorder although the vaccine itself by causing a toxic effect to Madison's nervous system could cause the chronic seizure disorder as well. Tr. at 56. In the undersigned's hypothetical that the vaccine did not cause the Kawasaki disease which arose coincidentally to the vaccination, Dr. Tornatore stated that Kawasaki was a predominant factor in causing Madison's seizure disorder but the vaccination was a substantial factor. Tr. at 57. Status epilepticus is atypical for Kawasaki. *Id.*

[12] However, just two weeks after her vaccinations, Madison tested positive for enterovirus on April 13, 2002.

Dr. Tornatore agreed with Dr. Bellanti, petitioners' immunologic expert, that because of the duration of Madison's first seizure, she would have been included in the National Childhood Encephalopathy Study (NCES).[13] Tr. at 66.

On cross-examination, Dr. Tornatore admitted that Kawasaki disease can present with febrile seizures. Tr. at 69. He agreed that Madison's current condition was related to her Kawasaki disease and to the vaccination. Tr. at 70. Not all of Madison's seizures were associated with fever. Tr. at 73.

Madison's pre-existing immune dysfunction was hypogammaglobulinemia. Tr. at 73-74. The gamma globulins are not the issue. The T-cell dysfunction is the issue because of its impact on the humoral arm of the immune system, making it more difficult for antigen clearance whether by antibodies or the cell-mediated component. Tr. at 74. An infection can trigger Kawasaki disease. Tr. at 75. Kawasaki is an inflammatory, autoimmune condition. *Id.* Madison's April 2003 MRI could be consistent with vasculitis. Tr. at 76. The MRI changes were due to either the Kawasaki or the ongoing seizure disorder. *Id.*

Respondent's counsel directed Dr. Tornatore to the PCR test of Madison's plasma on April 13, 2002 which detected enterovirus two weeks after her vaccination. Tr. at 78. Enterovirus can cause fever. *Id.* Enterovirus can cause upper respiratory infection. *Id.* Enterovirus can cause nasal congestion. *Id.* Around the end of March 2002, Madison's brother and mother were sick with fever and cough. Tr. at 83-84. But enterovirus would not cause status epilepticus. Tr. at 84. Dr. Tornatore stated that the synergy of the enterovirus and four antigens

[13] However, the NCES dealt with whole-cell DPT, not acellular DPT, and the authors attempted to weed out anyone with a prior medical abnormality.

(diphtheria, pertussis, tetanus toxoid, and haemophilus B influenza) was a probable scenario in an immunologically-challenged child that would lead to subsequent persistent fevers and seizures. Tr. at 91. Madison still had some nasal congestion on April 5, 2002. Tr. at 92.

Dr. Tornatore agreed that if Madison had been exposed to enterovirus antigen, it would be hard for her to clear it from her body. Tr. at 95. If Madison had had an enteroviral infection when she received acellular DPT and HiB vaccines, Dr. Tornatore would think both the infection and the vaccines were substantial factors in causing her fever and seizure. *Id.* If Dr. Tornatore added in the Kawasaki disease, and assumed that the enterovirus caused the Kawasaki disease, he would say that all four factors (the two vaccinations, the enterovirus, and the Kawasaki disease) were substantial factors in causing Madison's fever and initial seizure. Tr. at 96. He leaned more toward the vaccination as the cause of the seizures because the enterovirus was subclinical and it would be hard for him to see how the enterovirus would suddenly blossom into an acute febrile illness leading to status epilepticus. *Id.* The vaccination was the tipping point pushing Madison over and causing the seizure disorder and, if we accept the enterovirus was there, in conjunction with enterovirus that led to the subsequent vasculitis. *Id.*

Dr. Tornatore said that enterovirus alone was not enough to cause the Kawasaki disease. Tr. at 97. Madison's immune response could not mount antibodies to the inciting antigen because the humoral arm of her immune system was not working well, but the cellular arm of her immune system was. So she had a cell-mediated response, but not an antibody response. Tr. at 97-98. The cellular dysimmunity causes chemokine and cytokine release which can cause vasculitis. The T-cells can infiltrate into the blood vessels and cause inflammation there. Tr. at 98-99. Her fever and prolonged convulsion are evidence of a cytokine storm. Tr. at 99.

Respondent's counsel and Dr. Tornatore then engaged in a discussion about whether Madison had an afebrile seizure as her first seizure because in petitioners' Exhibit 2, p. 45, Dr. Chacon records there was no fever before her first seizure. Tr. at 100. Since Dr. Chacon wrote what Madison's mother told him, the undersigned called Kimberly Burshiem, Madison's mother, to testify. Tr. at 111.

Kimberly Burshiem testified that Madison received the vaccination about 3:00 p.m. and was fussy that night and the next day. She remembered having to hold her a lot. She believed Madison's seizures began around 7:00 p.m. the following day. Tr. at 111-12. Her seizure lasted about an hour and the ambulance helper thought she had a little fever. Tr. at 112. Between the time of vaccination and the time of Madison's first seizure, Ms. Burshiem felt Madison had a fever but she did not take her temperature. *Id.* Madison felt hot to the touch. However, Ms. Burshiem did not have a thermometer. *Id.*

When Ms. Burshiem spoke to Dr. Chacon on March 29th, she told him that she had not taken Madison's temperature. She believes she told him that Madison felt hot. Tr. at 113. She did not tell anyone that Madison did not have a fever. She told them that she did not know if Madison had a fever because she did not have a thermometer. Tr. at 114.

Ms. Burshiem felt that Madison was fussy and warm. She was warm that day but got really fussy right before the seizure. Tr. at 119. Ms. Burshiem thought to herself she had better go get a thermometer to see if Madison had a fever. Tr. at 119-20. She laid Madison down to walk out the door. Tr. at 120. Madison had started to feel warm in the middle of the day. *Id.* Ms. Burshiem was also going to buy Tylenol with the thermometer. Tr. at 121.

Dr. Tornatore resumed testifying and said that, considering Madison was immune deficient, when she got fussy and had a fever, she was having an immune-mediated response. Tr. at 122-23. Dr. Tornatore stated that HiB vaccine could also cause temperature rise and it would be impossible to choose between the acellular DPT and the HiB as the cause of Madison's fever. Tr. at 124. Madison was exposed to six antigens, including the polio vaccine and the enterovirus, and she was not immunologically capable of producing antibodies. Tr. at 125.

Dr. Tornatore testified that, in both typical and atypical Kawasaki disease, febrile seizures are extremely rare. Tr. at 126. The scarce medical literature on Kawasaki disease seizures discusses children with really profound neurologic symptoms, such as anorexia and progressive deterioration of consciousness. Tr. at 127. The case reports discuss more than a febrile seizure. *Id.* Madison had the seizure and was reported as fine a couple of days later, smiling, happy, and looking good. That is not consistent with Kawasaki significantly involving the nervous system in the case reports. Tr. at 128. The literature shows that 1 out of 200 children with Kawasaki will have central nervous system involvement or 0.4%. *Id.* Vasculitis of the nervous system because of Kawasaki disease in the two case reports is bad and progressive. The child in the case reports has a seizure because he or she has inflammation of the blood vessels in the brain. *Id.*

Dr. Tornatore admitted that Kawasaki disease can rarely present with febrile seizures. Tr. at 129. It is also rare for acellular DPT to cause an acute neurologic injury. *Id.* Madison's treating immunologist Dr. Schiff recommended that Madison's pediatrician submit a vaccine adverse event report (VAERS) about Madison. Tr. at 130. He thought Madison had a possible adverse reaction to her vaccinations. *Id.* We do not usually see this in medical records. Tr. at 131.

Dr. Joseph A. Bellanti, an immunologist, testified next for petitioners. Tr. at 136. He directs the International Center for Interdisciplinary Studies of Immunology. *Id.* His main research interests are antimicrobial immunity and antibody, humoral, and cell-mediated responses to vaccines. Tr. at 137. He is also studying a new recombinant anthrax vaccine, immune responses to it, and possible reactogenicity. Tr. at 138. He is working on the fourth edition of his textbook on immunology and has published over 400 peer-reviewed articles. *Id.* He has been president of the Society for Pediatric Research, the American College of Allergy and Immunology, the Inter-Asthma Organization, and the American Association of Laboratory Immunology. Tr. at 138-39. He has been editor in chief of the journals "Pediatric Research," "Annals of Allergy," and "Allergy and Asthma Proceedings." Tr. at 139.

Dr. Bellanti thinks this is a very complex case with multiple factors converging on Madison at eight months of age when she received the vaccine. *Id.* He thinks the vaccine was the triggering point that tipped Madison over the balance toward a cascading set of events, leading to her initial convulsion and subsequent chronic set of convulsions or epilepsy from which she now suffers. Tr. at 140. Kawasaki disease has an unknown etiology but many suspected triggers. *Id.* It is a response of inflammation or a vasculitis that causes rash and obliteration of the coronary vessel, but primarily affects the mucous membranes, the eyes, and the mouth. It can also involve the central nervous system. *Id.* Kawasaki is an immune-mediated disease. *Id.* Several bacterial and viral agents, such as measles, parvovirus, herpes, and Epstein-Barr, have been implicated as triggers and so have some vaccines. Tr. at 141. Anything that stimulates the immune system in all its dimensions can be a trigger for Kawasaki. *Id.*

Madison had an immune deficiency at the time she was vaccinated. *Id.* During her first six months of life, Madison's mother's antibodies (IgG) protected her against bacterial infections. Tr. at 142. Because Madison was breastfed, she also had antibody protection (IgA). *Id.* When Madison's gamma globulin from her mother declined, she never made back the level and it continued to decline so that, at eight months, it was very low. Tr. at 142-43. She was below 150 for all the gamma globulins. Tr. at 143. Madison had primarily a B-cell problem (humoral immunity) with some evidence of T-cell abnormalities. She had a low CD3 and CD4. She had maturational hypogammaglobulinemia. *Id.*

At eight months, she was at her most vulnerable and, if she were exposed to enterovirus or bacteria, she would be susceptible. Tr. at 144. It was not until she received the vaccines that, within 24 hours, catastrophe occurred. *Id.* She had the convulsion due to the endotoxin in the acellular DPT. The endotoxin could have sensitized her to the subsequent development of Kawasaki. Tr. at 145. Endotoxin is a very potent Th1 stimulant. Lipopolysacharide is the main component of endotoxin and is a very strong stimulant of TH1 responses. That could have initiated the vasculitis, and whatever caused the Kawasaki disease on its own would be enhanced by that added burst of endotoxin from the acellular DPT. *Id.*

Dr. Bellanti said that Madison's prolonged excretion of enterovirus was consistent with her agammaglobulinemia.[14] *Id.* People with immune deficiency cannot balance cytokines, making them more susceptible to infections or diseases. Tr. at 147. Dr. Bellanti thinks the theory behind the injury is the innocent bystander. When Madison developed Kawasaki disease, and received a vaccination, the vaccine stimulated her immune system, releasing pro-

[14] Madison actually had hypogammaglobulinemia, not agammaglobulinemia.

inflammatory cytokines, which is vasculitis affecting the blood vessels. Tr. at 147-48. Vasculitis in the brain causes the white matter to be demyelinated and destroyed. Tr. at 148. The initial insult to Madison's brain was due to the acellular DPT vaccine endotoxin. *Id.* Dr. Bellanti has had some child patients with epilepsy and most have an epileptogenic focus. Tr. at 149. That means they have a bit of destruction in the brain that becomes active when there is a stimulus, which could be too much salt, or fever, or any number of insults that cause the focus to fire, causing repeated convulsions. *Id.* Dr. Bellanti believes Madison had a series of cascading events--hypogammaglobulinemia, subsequent infection, viruses--but the main trigger that tipped the balance was the acellular DPT vaccine. *Id.* Tr. at 151.

Dr. Bellanti stated that the vaccines were substantial contributing factors in causing Madison's seizure disorder. Tr. at 150. The enterovirus did not affect Madison's central nervous system, but was just present in her blood stream for a prolonged period of time. *Id.* The manifestations of Madison's Kawasaki disease occurred after her vaccinations. Tr. at 152. The rash was not detected until April 11th. Madison was given gamma globulin as a treatment for her Kawasaki disease and she improved. *Id.*

Dr. Bellanti said that Madison's Kawasaki disease was atypical in that she did not have conjunctivitis, oral lesions, or coronary involvement. She did have rash, fever, and good response to intravenous gamma globulin. Tr. at 153. Kawasaki is a syndrome of unknown etiology. *Id.* Madison had delayed myelination of her brain. Tr. at 155.

On cross-examination, when asked if Kawasaki disease would explain everything that happened to Madison, Dr. Bellanti responded that Madison's prolonged convulsions were a bit unusual for Kawasaki. Tr. at 156. Convulsions can be included in atypical Kawasaki disease.

Tr. at 157. Madison was protected by maternal IgG and did not have infections before her vaccinations. Tr. at 158.

Six months before the vaccinations at issue in this case, Madison went to the emergency room on October 8, 2001 with 100.4º fever. Tr. at 159. She had thrown up four times and had an increased temperature as well as congestion that day. Tr. at 160. Dr. Bellanti doubted that this was the beginning of her Kawasaki disease because upper respiratory infections are very common in this age group particularly with a two-year-old brother in day care. *Id.* This was not a serious infection. Tr. at 161. A child with hypogammaglobulinemia has more serious bacterial infections affecting the middle ear, the throat, and the skin, as in pneumonia, and more serious ones involving joints, as in septic arthritis. *Id.* Madison was 11 days short of two months or six weeks of age at the time of her October 2001 emergency room visit. Tr. at 162.

Vasculitis occurs following vaccinations and Kawasaki disease is a vasculitis. Tr. at 165. Dr. Bellanti thinks that vaccinations caused Madison's convulsions and may have contributed to the Kawasaki disease, but we do not know what causes Kawasaki disease. *Id.* We know it is a vasculitis and DPT can cause a vasculitis. Vasculitis is more common in children with hypogammaglobulinemia. *Id.* He does not know if Kawasaki disease was simmering in Madison before she received her vaccinations. Tr. at 166. Clinically, Madison did not have any manifestations of Kawasaki disease when she received the vaccinations on March 28, 2002. *Id.* Dr. Bellanti does not know if Kawasaki disease would have occurred even if Madison had not received DPT, but he felt that the vaccine probably contributed to her fever, her convulsions, and her prolonged convulsive disorder, and possibly enhanced the progression of her Kawasaki disease. Tr. at 168.

Dr. Bellanti said he did not know when Madison's Kawasaki disease began but it became clinical 14 days after vaccination. Tr. at 168, 169. The initial abrupt onset of fever after Madison's vaccinations was due to the vaccinations. Tr. at 169, 170. The initial fever was due to the endotoxin in the acellular DPT vaccine. Tr. at 171. The endotoxin promoted a vasculitis which started a cytokine-mediated injury that sustained the fever afterwards. *Id.* The vasculitis started within a few days of vaccination. *Id.* Madison's subsequent fevers, but not the initial fever, was due to her vasculitis. Tr. at 172. Madison did not spike fevers during her first hospitalization which ended April 8th, but did spike fevers during her second hospitalization. Tr. at 174, 176. There were two phases: the first convulsive episode was due to the endotoxin in the acellular DPT vaccine; the second phase was when Madison went home and had more fevers which could have been due to the inflammatory response of the vasculitis. Tr. at 177. The vaccine caused the initial convulsion, convulsive disorder, and the brain injury, was involved in vasculitis, and probably contributed to the ongoing process of Kawasaki which involves vasculitis. Tr. at 177-78. Madison was probably having vasculitis before the clinical symptoms related to Kawasaki disease and the vaccine contributed to it. Tr. at 178.

Kawasaki is a vasculitis and DPT can cause vasculitis. Tr. at 179. Children with hypogammaglobulinemia are more prone to vasculitis because they cannot clear antigens. *Id.* Madison was eight months of age when the maternal antibodies were gone and all these things happened to her: enterovirus, DPT, vasculitis, and atypical Kawasaki. Tr. at 179-80. Dr. Bellanti did not think that Madison's emergency room visit with congestion and fever at six to eight weeks of age was the onset of her Kawasaki disease. Tr. at 180. If Dr. Bellanti accepted that Madison's onset of Kawasaki preceded her DPT vaccination, he thought DPT possibly

significantly aggravated it. Tr. at 181. He thought that Madison's mother's antibodies would still have protected her at the age of eight weeks. *Id.*

Dr. Russell D. Snyder, a pediatric neurologist, testified first for respondent. Tr. at 182. His opinion is that Kawasaki disease caused Madison's condition. Tr. at 184. Her first seizure the day after she received acellular DPT was variously described as lasting 20 minutes, 30 minutes, and one hour. Tr. at 185. She was seizing on arrival to the ER on March 29, 2002. *Id.* Madison was encephalopathic but not for a duration of 24 hours. Tr. at 186. There was no indication at the time that her seizure on March 29, 2002 caused her any permanent neurological injury. Tr. at 187. If it had, Dr. Snyder would have expected that Madison would not have returned to her pre-seizure state. *Id.* Her CT scan, brain MRI, and EEG were normal. *Id.*

Dr. Snyder regards the evidence as slim that acellular DPT causes Kawasaki disease because immunization is ubiquitous and Kawasaki is rare. Tr. at 188. He did not think that Madison's abnormal immune system prior to her immunizations had any particular impact because, if it had, she would have mounted less of a response to the immunization rather than more. *Id.*

Dr. Snyder described Madison's first seizure as prolonged and febrile. Tr. at 189. She had a number of factors that could produce fever: enterovirus, immunization, and Kawasaki. *Id.* We do not know for sure when her Kawasaki began and it may well have been before the first seizure. Tr. at 190. Madison could easily have been incubating Kawasaki disease at the time she received her immunizations on March 28, 2002. *Id.* Enterovirus has been thought to be associated with Kawasaki disease. *Id.* Enterovirus has also been thought to be associated with febrile seizures. *Id.* It is rare for Kawasaki disease to present with a febrile seizure. Tr. at 191.

Because of her positive PCR in April 2002, Madison had enterovirus at that time. *Id.* We do not know when the onset of Madison's enterovirus was. Tr. at 192. Madison had nasal congestion and a fever, and other family members had respiratory illness. Tr. at 192-93.

Kawasaki disease was becoming manifest during the course of her hospitalization in April 2002. Tr. at 193. Aside from her immune problem, Kawasaki disease explains everything that happened to Madison, including her intractable seizure disorder and developmental delay. Tr. at 193-94. Madison's brain MRI in April 2003 showing hypomyelination is explained by Kawasaki because it manifests as cerebral vasculitis. Tr. at 194. There is no evidence in the medical literature that acellular DPT causes vasculitis. *Id.* Dr. Snyder's experience with local conferences and the national meetings in his specialty prompt him to disagree with the opinion that acellular DPT causes vasculitis. Tr. at 195. Madison's vasculitis was due to Kawasaki disease. *Id.* Vasculitis is a known feature of Kawasaki disease, but not a known feature of acellular DPT. Tr. at 196.

Dr. Snyder stated that acellular DPT did not trigger Kawasaki disease in Madison. *Id.* Acellular DPT is so ubiquitous that he would see an association between it and Kawasaki if it occurred. *Id.* Madison's initial white blood cell count was elevated. Tr. at 196-97. Enterovirus can cause a rash and encephalopathy if there is a direct viral invasion. Tr. at 197. Enterovirus was never detected in Madison's cerebrospinal fluid and, therefore, she never had encephalitis from the virus or a direct infection within her nervous system from the virus. Tr. at 198.

Dr. Snyder said that Kawasaki disease is an immune response to certain inciting types of agents but not a direct infectious disease. *Id.* The Institute of Medicine would not conclude that acellular DPT caused Madison's seizure because there were other causes that could be found. Tr.

at 201-02. Dr. Snyder did not agree that acellular DPT can cause chronic seizure disorders in children. Tr. at 203. He agreed that acellular DPT can cause febrile seizures. *Id.* He said that if a child has an acellular DPT followed by a febrile seizure, if the child has subsequent seizures, some underlying condition causes those subsequent seizures. Tr. at 203-04. There is a genetic predisposition to develop febrile seizure. Tr. at 204. Dr. Snyder agreed that whatever causes the initial fever triggers the manifestation of that condition. Tr. at 204-05. Dr. Snyder calls this condition "generalized epilepsy with febrile seizures plus" meaning plus other types of seizures. Tr. at 205. SCN1A and other genes are involved. Tr. at 206.

Dr. Snyder agreed that people have a genetic predisposition to develop Kawasaki syndrome. Tr. at 208. There are things associated with the onset of Kawasaki, such as enterovirus. *Id.* Many infectious agents can trigger Kawasaki. Tr. at 209. No medical literature convinces Dr. Snyder that vaccines can trigger Kawasaki. *Id.*

Dr. Snyder stated that the vaccine may have contributed to the fever that caused Madison's first seizure. Tr. at 210. He agreed that some children can develop chronic seizure disorders from a single injury or insult. Tr. at 213. This assumes some focus of injury. Tr. at 213-14. In general, what caused the first seizure causes the subsequent seizures. Tr. at 214.

Kawasaki disease's symptoms include fever and rash, both of which were present in Madison. Tr. at 214-15. The rash occurred during the fourth hospitalization (counting the October 1991 ER visit, the first visit to Baptist Hospital on March 29, 2002, the second visit to Baptist Hospital on April 9, 2002 with a transfer on April 10, 2002 to Miami Children's Hospital) from April 10-20, 2002. Tr. at 215. But Madison did not have mucosal changes, cervical lymphadenopathy, or cardiac problems. Tr. at 216. However, she did have a response to

IVIG therapy. *Id.* She did not have conjunctivitis. Tr. at 217. There are two cases per 1,000 of Kawasaki disease involving febrile seizures. *Id.* Most of the time, no specific cause is found for vasculitis. Tr. at 219. The authors of the medical article describing two febrile cases among 1,000 cases of Kawasaki disease state that they expected there to be a lot of febrile seizures because of the very high fevers in Kawasaki, but they found only two cases. Tr. at 222.

Dr. Snyder cannot say when Madison first had enterovirus. Tr. at 225. The only way enterovirus could cause a seizure would be by causing a fever. Tr. at 226. There is no evidence of focal brain injury in this case. Tr. at 227. Acellular DPT could have been a contributory factor in triggering Madison's first seizure. Tr. at 229. Madison may have been harboring enterovirus before she received her March 28, 2002 vaccinations and given enterovirus to her family or the other way around. Tr. at 230. Dr. Snyder agreed that when a child has a febrile seizure and then subsequent seizures, a brain MRI may not show focal brain injury. Tr. at 231. He agreed that whatever caused the first seizure caused the ongoing chronic seizure disorder even without evidence of focal brain injury. *Id.* If in this case, there were no enterovirus, no Kawasaki disease, and no immune deficiency, Dr. Snyder would agree that the vaccination triggered the first seizure. Tr. at 231-32. If he added back into the equation the hypogammaglobulinemia, his opinion would not change. Tr. at 232. If he added back into the equation the subclinical enterovirus, it would have contributed as a fever trigger. Tr. at 232-33.

Dr. Brian Ward, an infectious disease specialist, testified next for respondent. Tr. at 238, 240. He has spent a lot of time studying vaccines and vaccine immune responses, but is not a formally trained immunologist. Tr. at 240. His opinion is that fever caused Madison's first seizure which evolved due to a combination of her enterovirus and Kawasaki disease persisting

for 12 months. Tr. at 241. He thinks the vaccine is known to elicit low-grade fever in some children and Madison was infected by enterovirus, which is one of the most common causes of febrile seizures. Tr. at 241-42. At least one member of Madison's family was ill and she had an upper respiratory tract infection. Tr. at 242. Fever is a classic symptom of enterovirus. Madison also had a runny nose and was fussy. *Id.* If Madison had not had the vaccination at the time and everything else were the same, people would think this was a classic presentation of enterovirus. Tr. at 243. Dr. Ward was surprised that none of Madison's treating physicians picked up on the PCR test results of enterovirus infection in the blood. *Id.* Madison's runny nose shows that she was incubating something just when she received the vaccine. Tr. at 243-44.

Dr. Ward stated that Madison's case was enormously complicated because of her possible immunocompromise. Tr. at 244. When a child has an immune system deficiency, whether T-cell or antibody, he agreed with Dr. Bellanti that she is much more likely to have transient difficulty in making antibodies. *Id.* Under those circumstances, her manifestations of common infections are not necessarily typical. *Id.* It would be useless to decipher which of her symptoms were typical or not of an enterovirus infection. Tr. at 244-45. Ten or 12 days after her initial hospitalization, Madison had a PCR positive for enterovirus infection. Tr. at 245. We do not know the date of her exposure to enterovirus. *Id.*

Dr. Ward said that we all agree that Madison was relatively well until the time she received her March 28, 2002 vaccinations. *Id.* His best guess is that her enterovirus manifested around the time she received acellular DPT and HiB vaccine and what we have here is a very unfortunate coincidence of timing. *Id.* Acellular DPT is known to be associated with mild fever.

Tr. at 246. There is no question in Dr. Ward's mind that the acellular DPT and HiB vaccinations may have contributed to her fever even if in fact she was incubating enterovirus at this time. *Id.*

Dr. Ward stated that fever is the cardinal diagnostic feature of Kawasaki, but the vaccine could not have caused Kawasaki in a day. Tr. at 246-47. He thinks it impossible to say whether Madison had Kawasaki disease at the time of her immunization. Tr. at 247. There is a known association between enterovirus infection and Kawasaki disease. *Id.* He admitted he did not have a clue when Madison's Kawasaki disease began. Tr. at 249-50.

Dr. Ward believed that Madison had an underlying viral infection that was on the verge of becoming manifest when she received a vaccination that boosted her fever a little bit. He did not think we would ever know how much each of these two initiating factors contributed to her fever. Tr. at 250. He includes the HiB vaccine as a contributing factor because any vaccine can cause mild fever. In studies of haemophilus B influenza vaccine, you see mild fevers, as you do with acellular DPT. *Id.* Any immunizing product might be expected to result in a mild fever in a small number of children. Tr. at 250-51. That is particularly true with inactivated vaccines. Tr. at 251. His opinion is that at least two of the three vaccinations plus her underlying enterovirus combined in a way he cannot separate to cause Madison's mild fever which led to her first seizure. *Id.*

Madison did not have any high spiking fevers during her first hospitalization from March 29 to April 8, 2002, but she received huge doses of Tylenol. Tr. at 252. She had persistent low-grade fever. Tr. at 253. He agrees that live vaccines are associated with Kawasaki, but not inactivated vaccines, according to the literature. Tr. at 254. The endotoxin in DPT and acellular DPT probably does contribute both to the mild fever and the efficacy of the vaccine. *Id.*

Dr. Ward said that if Madison had never received her third acellular DPT, all the events that occurred could be completely explained by her underlying immunologic difficulties and the enteroviral infection. Tr. at 258. However, if the enterovirus were not there and only the vaccinations, Dr. Ward said he could not get beyond the acellular DPT vaccine's and HiB vaccine's causing the first febrile seizure. Tr. at 259.

When Madison received her March 28, 2002 vaccinations, she was exposed to five antigens (pertussis, tetanus, diphtheria, haemophilus B influenza, and polio). Tr. at 260. Madison was a little bit more fragile because she had difficulty eradicating an enterovirus over a period of a year. Tr. at 262. After the vaccinations, she became symptomatic of enterovirus whereas before the vaccinations, she was not. *Id.* Madison was later found not to have decent humoral responses to the vaccine antigens so she did not respond as expected to the vaccines. Tr. at 264. She made very low titers of antibodies to diphtheria and tetanus toxoids. *Id.* Neither acellular DPT nor HiB is known to have any direct immunosuppressive effect on anybody. Tr. at 264.65. There is no evidence of a cytokine storm in Madison's case. Tr. at 266.

Dr. Ward thought that Madison's persistent fever was the result of a persistent enterovirus infection. Tr. at 267. Madison was well until a day or two of her March 28, 2002 immunizations. Tr. at 268. Several of her family members were ill at the time. *Id.* If she had some degree of hypogammaglobulinemia, one would expect that was the time she acquired enterovirus (in the week preceding her vaccinations). *Id.* This was early spring when enteroviruses are known to proliferate. *Id.* The vast majority of fevers associated with inactivated vaccines are gone within 24 hours. Tr. at 268-69. Her persisting fevers were not related to her immunizations, but to her enterovirus. Tr. at 269.

Dr. Ward had some doubts that Madison had Kawasaki disease or even vasculitis. Tr. at 270. He did not know the cause of Madison's abnormal brain MRI in April 2003 although persistent enterovirus was a possible cause as well as Kawasaki. *Id.* At the time Madison was vaccinated on March 28, 2002, she did not have fever, fussiness, or runny nose. Tr. at 271. Even with a child with hypogammaglobulinemia, the vaccines can cause a febrile reaction. Tr. at 272. We have no idea when Madison developed enterovirus. Tr. at 272-73.

Dr. Ward agreed that Kawasaki disease is an autoimmune disease. Tr. at 277. Ten days would be an appropriate timeframe for causation of an autoimmune disease after an antigenic stimulus. Tr. at 277-78. Dr. Ward does not know if Madison had Kawasaki disease. Tr. at 278. If she had it, it was atypical. *Id.* The most common cause of fever in the spring which is culture-negative as in Madison's case is enterovirus. Tr. at 279. Inactivated vaccines can cause febrile seizures within one to three days. *Id.*

Dr. Ward stated there are many different enteroviruses but all are known to be neurotropic. Tr. a 281. He recognized that Madison's test of her cerebrospinal fluid was negative for enterovirus, meaning the virus had not entered her brain, but he said that the test achieves only about a 50 to 60 percent positivity. Tr. at 282.

At that point, the undersigned discussed Herkert v. Secretary of HHS[15] in which an 18-month-old child received acellular DPT and was cranky the night of vaccination which both sides' experts attributed to the vaccination. Tr. at 284. The next morning, he was limp like a rag doll. He had a cervical section transverse myelitis, making him quadriplegic, and his palms were red. It turned out the whole family had cytomegalovirus, which the child had been harboring. *Id.*

[15] No. 97-518V, 2000 WL 141263 (Fed. Cl. Spec. Mstr. Jan. 19, 2000).

Testimony from petitioners's expert in Herkert was that the acellular DPT vaccination caused immunomodulation in the child which enabled the cytomegalovirus he was harboring to cause the transverse myelitis. The undersigned held for petitioners and the decision was not appealed. Tr. at 285.

The undersigned also discussed Nash v. Secretary of HHS[16] in which a child came to the pediatrician with a fever due to an undiagnosed pneumococcal infection, and received whole-cell DPT. He had a higher fever after the DPT vaccination and was hospitalized with pneumococcal meningitis. *Id.* Testimony from petitioner's expert in Nash was that the DPT modulated the child's immune system so that he could no longer fight off the latent pneumococcal infection which became clinical and much worse, causing meningitis. The undersigned held for petitioner and the decision was not appealed. *Id.*

The undersigned said that a reasonable understanding of this case is that Madison was harboring an enterovirus without any clinical symptoms before her vaccinations on March 28, 2002. *Id.* As a consequence of the vaccinations, she became mildly feverish. The other effect of the vaccinations was to make patent the subclinical enterovirus so that Madison developed symptoms of an upper respiratory infection (runny nose). Tr. at 285-86. Together, the acellular DPT and HiB vaccinations were substantial factors with the enterovirus, another substantial factor, in causing Madison's first fever that led to her seizure. Tr. at 286. Subsequently, the enterovirus either caused atypical Kawasaki disease or did not cause Kawasaki disease, depending on whether or not she had it. Dr. Ward did not think she had it because the enterovirus itself could explain Madison's fever spikes which ultimately became worse and

[16] No. 00-149V, 2002 WL 1906501 (Fed. Cl. Spec. Mstr. June 27, 2002).

worse. *Id.* Her subsequent brain MRI a year later was abnormal and was a consequence of her repetitive seizures. Without the vaccinations' modulating her already poorly-functioning immune system, this would not have occurred. *Id.* The undersigned ruled on the record for petitioners. *Id.*

If the undersigned left out the Kawasaki disease, we have three factors–the enterovirus, the acellular DPT, and the HiB–all of which can cause fever. None of the experts denied this. Two to three weeks after the first febrile seizure, Madison's fevers started to spike. That is not explainable from the vaccinations so something else was going on. Tr. at 287. The vaccines worsened Madison immunologically because she could not fight off the enterovirus although she was doing a good job of it before the vaccinations because she was asymptomatic before she received them. Tr. at 288. As a result of the synergy between all three (the enterovirus and acellular DPT and HiB vaccines), the enterovirus gained steam. *Id.*

The undersigned held that Madison's chronic seizure disorder was related to her first seizure. Tr. at 289. Whether the enterovirus acted with or without Kawasaki, which it may or may not have caused, seems irrelevant. The undersigned held that all three: the enterovirus, the acellular DPT vaccine, and the haemophilus B influenza vaccine–were substantial factors causing Madison's fever within 24 hours of her vaccinations, causing her seizure. Tr. at 289-90. The undersigned held that there was a biologically plausible medical theory, a logical sequence of cause and effect, and a medically appropriate time sequence between the vaccinations, the harboring of the subclinical enterovirus, the worsening or significant aggravation which made the enterovirus symptomatic, combining with the vaccinations to cause the fever causing the seizure

which was long, leading to subsequent seizures and the repetitive, high fevers, causing brain damage and subsequent sequelae. Tr. at 290-91.

Respondent's counsel asked for a written opinion. Tr. at 291.

DISCUSSION

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

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

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

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

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

Petitioners must show not only that but for the vaccine or vaccines, Madison would not have had her first seizure and a seizure disorder, but also that the vaccine or vaccines was/were a substantial factor in bringing about her first seizure and seizure disorder. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

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

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

35 F.3d at 549.

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

The Federal Circuit in Capizzano emphasized the opinions of petitioner's four treating doctors in that case. 440 F.3d at 1326.

This case concerns fever after acellular DPT and HiB vaccinations, followed by a 45-minute seizure, chronic encephalopathy, and developmental delay. The undersigned has ruled before that acellular DPT may cause a fever prompting a seizure followed by a seizure disorder. See Noel v. Secretary of HHS, No. 99-538V, 2004 WL 3049764, *17 (Fed. Cl. Spec. Mstr. Dec. 14, 2004). See generally McMurry v. Secretary of HHS, No. 95-682V, 1997 WL 402407 (Fed. Cl. Spec. Mstr. June 27, 1997) (whole cell DPT caused fever causing seizure and seizure disorder).

Of the four expert witnesses, only Dr. Ward, respondent's infectious disease expert, was doubtful that Madison had Kawsaki disease, mindful that she was diagnosed with atypical Kawasaki disease because she did not have all the symptoms of the classic Kawasaki disease. Dr. Ward thought that all that happened to Madison was explainable by her having enterovirus infection. On the other hand, respondent's neurologic expert Dr. Snyder based his entire opinion on Madison's having Kawasaki disease because he attributed her first seizure, her seizure disorder, and her brain injury to Kawasaki.

As everyone accepted, this is a very complex case because of the convergence of four factors upon Madison at almost the same time. She probably was exposed to enterovirus since subsequent to her initial febrile seizure and consequent hospitalizations, she tested positive by

PCR for enterovirus. She did not clear this infection for a year. No one knows when she contracted enterovirus, but evidence shows that her older brother and mother had some respiratory difficulty just before Madison received her March 28, 2002 HiB and acellular DPT vaccinations (the undersigned omits discussion of Madison's inactivated polio vaccination because no one at the hearing attributed anything to it although Dr. Ward testified that any vaccination can cause fever).

All the witnesses accept that Madison was symptom-free when she received her March 28, 2002 vaccinations. Within 24 hours, she was irritable and warm. All the witnesses accept that the HiB and acellular DPT vaccinations contributed to her fever. Madison developed a runny nose subsequently, but not fever spikes until her second hospitalization, a couple of weeks after her vaccinations. This confirms to the undersigned that, although respondent's expert Dr. Snyder testified that Madison's Kawasaki disease caused her first seizure, the Kawasaki disease was not clinically manifest until after her initial seizure.

The undersigned accepts that it is reasonable for Madison to have been exposed to enterovirus (which has been associated with Kawasaki disease) but did not clinically manifest enterovirus at the time she was vaccinated with HiB and acellular DPT vaccines. In addition to these factors, Madison was immunodeficient. She could not get rid of antigens, hence her harboring enterovirus in her blood for a year, according to the positive PCR tests. But the enterovirus did not invade her cerebrospinal fluid, which means that the enterovirus did not invade her brain and cause her brain injury. Dr. Ward disagreed on the lack of effect of enterovirus on Madison's central nervous system (her brain) because he said that 40 to 50 percent of the time, the PCR of the cerebrospinal fluid will yield a false negative, but the undersigned is

in no position (and Dr. Ward is in no position) to say that this is the time that the negative PCR of Madison's cerebrospinal fluid was a false negative and she actually had enterovirus infection of her brain.

The course that seems most reasonable to the undersigned is this: in late March 2002, Madison was exposed to enterovirus (the alternative is that she had been carrying the virus even before then and actually gave it to her brother and mother) but did not develop clinical symptoms of enterovirus. She could not get rid of the enterovirus because of her hypogammaglobulinemia (too little gamma globulin). She received HiB and acellular DPT vaccinations on March 28, 2002 which, together with the enterovirus she was harboring, put more of a burden on her immune system and she developed irritability and a fever, resulting in her first febrile seizure lasting from 20 minutes to an hour, depending on the record notation.

Madison spent a week and a half in the hospital, was released home, and within a day, was back with fever and more seizures. Baptist Hospital could not deal with her continuing fevers and transferred her to Miami Children's Hospital on April 10, 2002, where her fever reached 107.5º. The spiking fevers were the beginning of her atypical Kawasaki disease. Although not all of Madison's many subsequent seizures were related to her many fevers, most were. A combination of the effect of the many seizures and her Kawasaki disease, caused her brain injury which appeared on her brain MRI a year later.

Respondent's theory, at least through Dr. Snyder, was that Kawasaki disease initiated Madison's initial seizure, but the medical literature that both parties filed does not support this proposition. The literature discussing the rare occurrence of seizures and encephalopathy in Kawasaki disease patients also discusses the reason for this rare central nervous system problem

in Kawasaki disease. Since Kawasaki disease is a vasculitis, it can cause subdural effusion, that is, leakage of cerebrospinal fluid into the brain, or it can cause vasculitis of dural vessels in the brain. Madison did not have either subdural effusion or vasculitis of the dural vessels in her brain as we can see from her initial MRI, which was normal. Her seizures, therefore, were not due to Kawasaki disease not only because the Kawasaki arose after her seizures began but also because there is no biologically plausible explanation for how Kawasaki disease caused her seizures if we look solely at the vascular component of the disease. Interestingly, the rate of febrile seizures among patients in the acute phase of Kawasaki disease is extremely low. This means that cerebral vasculitis and/or subdural effusion occurs rarely in Kawasaki disease, which is a syndrome known more for coronary vasculitis. Madison had neither cerebral vasculitis nor subdural effusion. Kawasaki had nothing to do with her seizures.

It is instructive to compare Madison's initial brain MRI, which was normal, with the brain CT scan and brain MRI of the little boy discussed in respondent's Exhibit H who had subdural vasculitis in his brain with seizures due to Kawasaki disease. He had an abnormal brain CT scan two days after onset of his seizures and an abnormal brain MRI eight days after onset of his seizures.

It also instructive to compare Madison's 2003 brain MRI, which was abnormal, with the brain MRI of the little girl discussed in respondent's Exhibit C (also Ex. JJ), whose brain MRI showed she had subdural effusion. Her brain MRI 12 months after the onset of her seizures showed diffuse and severe cerebral atrophy, characterized by enlargement of sulci and ventricular dilatation. This contrasts with Madison's CT scan and brain MRI two weeks after vaccination which were normal and with her brain MRI 12 months after the onset of her seizures which

showed no abnormality except for a delay in myelination. A subsequent MRI showed neuron death and an increase in myelination. A CT scan more than two years after the onset of Madison's seizures showed no extra-axial fluid collection and her ventricles were at the upper limits of normal. A brain MRI done two and one-half years after the onset of her seizures showed no extra-axial fluid collection and normal ventricles. Madison never had subdural effusion and enlargement of her sulci as the little girl in the case report did.

Clearly, from the literature describing the rare occurrence of encephalopathy and seizures in individuals with Kawasaki disease due to subdural vasculitis or effusion, their brain MRIs show the devastation of the inflammation of their brain blood vessels and the presence of the leakage of fluid into their brains. Early and late MRIs and CT scans show that Madison's brain vessels were not inflamed and there was no extra fluid in her brain. Thus, based on the literature that respondent filed pertaining to the rare instances when Kawasaki disease can cause convulsions and encephalopathy, Madison's experience with Kawasaki disease would not fit within those case analyses. Her Kawasaki experience spared the inflammation and fluid leakage that can rarely occur. What did occur was fevers, but it was her vaccinations, specifically acellular DPT and HiB, that caused her initial seizure and seizure disorder.

Respondent submitted an article discussing hypotheses about the cause of Kawasaki disease (immune impairment) and its clinical features, including extreme irritability, aseptic meningitis, and sensorineural hearing loss (Ex. C, second article). Madison was indeed immune-impaired and extremely irritable when she was brought to Baptist Hospital with seizures and fever, but she never had aseptic meningitis or hearing loss. Of note, the authors of this major discussion on Kawasaki disease never mention Kawasaki causing seizures.

Respondent submitted an article on enterovirus-caused meningoencephalitis with white matter abnormalities on MRI (Ex. KK). CT scan revealed fluid collection in the frontal extracerebral space of the five children with Kawasaki disease (which was 3.7% of the authors' 138 patients). But Madison did not have meningoencephalitis and she did not have fluid collection in the frontal extracerebral space. Moreover, the RT-PCR test for enterovirus RNA in Madison's cerebrospinal fluid one year after her onset of seizures was negative even though it was positive in her whole blood four months later in August 2003, showing that enterovirus had never entered Madison's brain and could not be responsible for her abnormal brain MRI one year after onset of her seizures.

Acellular DPT and HiB vaccines can cause fever. Although acellular DPT's rate of reaction is lower than whole-cell DPT vaccine, the literature shows that fever does occur in 25% of vaccinees. As the undersigned discussed at the end of the hearing in this case, the effect of DPT vaccine, whether acellular (Herkert) or whole-cell (Nash), can cause or increase fever and lead to worsening of an underlying viral (Herkert) or bacterial (Nash) infection.

Shyface is a case quite similar to Madison's case, concerning two-month-old Cheyenne Shyface, who was vaccinated with whole-cell DPT at the time he was harboring the beginning of E. coli infection, each of which could and did cause fever that rose to 110º, causing his death four days later. 165 F.3d at 1345. Respondent defended that the E. coli infection was the cause of the baby's fever and death. Testimony from the petitioners' doctor was that both the vaccine and the infection were equally responsible for the fever and death. The Federal Circuit held that each of the two factors (the vaccine and the infection) was a substantial factor in causing Cheyenne Shyface's very high fever and death, and but for the presence of each of these two factors, the

baby would not have had the high fever and would not have died. The Federal Circuit ruled in favor of petitioners even though petitioners did not prove that DPT vaccine was the only or predominant cause of his death. *Id.* at 1353.

In the instant action, all the experts agreed that HiB and acellular DPT vaccines contributed to the fever that caused Madison's first seizure. Petitioners' experts testified that the vaccines were substantial factors causing the fever that caused her first seizure and seizure disorder and, but for the vaccinations, she would not have had the fever and the first seizure and seizure disorder. Respondent's experts disagreed with the "but for" testimony and, depending on the expert, opined that the enterovirus was all that Madison needed to have the course she followed (Dr. Ward's testimony) or the Kawasaki disease was all that Madison needed to have the course she followed (Dr. Snyder's testimony). The undersigned finds that petitioners' experts are more credible on this point. First, it does not help the persuasiveness of respondent's argument against the vaccinations' being substantial factors in causing Madison's first fever, initial seizure, and seizure disorder that respondent's experts do not agree with each other over what the known factor unrelated to the vaccinations is (enterovirus? Kawasaki disease? both) that is itself a substantial factor. Secondly, since respondent's experts agreed that whatever the non-vaccine factor was (Kawasaki or enterovirus or both), they both agreed that the acellular DPT vaccination and HiB vaccination contributed to Madison's first febrile seizure.

Dr. Carro, a treating immunologist at Miami Children's Hospital, wrote on December 27, 2003 that Madison had delayed receiving further vaccination because of her seizures due to vaccine-induced fever. Many of Madison's doctors diagnosed her with atypical Kawasaki disease. The Federal Circuit in Capizzano emphasized taking the opinions of treating doctors

seriously. Therefore, the undersigned must give weight to both the treating doctor's opinion that Madison's fever was caused by her vaccinations and led to her seizures, and to Madison's treating doctors' opinions that she had atypical Kawasaki disease.

Dr. Bellanti had a plausible explanation for how acellular DPT may have exacerbated Madison's Kawasaki disease because endotoxin is composed of lipopolysacharide which very strongly stimulates TH1 responses which would enhance the vasculitis that is the hallmark of Kawasaki disease.

But it makes no difference to the undersigned whether Kawasaki disease was caused by the enterovirus or by the vaccine, or was caused by the enterovirus and worsened by the vaccine. There is an old principle in tort law that you take your victim as you find him. The undersigned holds that the vaccinations were substantial factors in causing Madison's seizure disorder based on the rarity of seizures appearing in Kawasaki disease and Madison's not having any sign of cerebral vasculitis or cerebral effusion on CT scan or initial brain MRI. Moreover, although a great many of her subsequent seizures occurred during fever, she also had seizures without fever, refuting the role respondent's expert Dr. Snyder has attributed to Kawasaki disease. Since Madison's experience with Kawasaki disease and incessant and high fevers came two weeks after vaccination, the undersigned accepts Dr. Bellanti's explanation that acellular DPT's endotoxin enhanced the Kawasaki disease, increasing its effect on Madison. The undersigned also accepts that the effect of the vaccinations was to make the latent enterovirus patent so that Madison had a runny nose after her first febrile seizure.

Respondent is liable for damages to petitioners because the vaccinations were substantial factors in causing Madison's seizure disorder which Kawasaki disease, through incessant fever

spikes, worsened when she had seizures associated with fever (and obviously was irrelevant when she had afebrile seizures). Respondent takes his victim as he finds her.

Congress' aim in passing the Vaccine Act was "to establish a Federal 'no-fault' compensation program under which awards can be made to vaccine-injured persons quickly, easily, and with certainty and generosity." H.R. Rep. No. 908, 99th Cong., 2d Sess. 3 (1986). If accepted tort law is that defendant takes his victim as he finds him, it would be strange indeed for Congress to intend in passing the Vaccine Act to make it harder for petitioners to prevail than if they were in the customary forum for resolution of tort claims. A look at tort law will be instructive for the parties.

In Jimenez Nieves v. United States, 618 F. Supp. 66 (D.P.R. 1985), plaintiff, who had diabetes mellitus, sued the United States under the Federal Tort Claims Act because of the negligence of the Social Security Administration in stopping payment on his mother's benefit checks (Social Security wrote the wrong date of her death in its records). Nieves was humiliated and suffered the stress of severe financial problems which had physical, mental, and emotional consequences. After Social Security dishonored the checks, plaintiff's diabetes worsened. He became depressed, impotent, and withdrawn, and deteriorated physically. Nieves became critically ill, almost blind, and totally disabled. By the time of trial, Nieves had had partial amputations of both feet and his renal functions had ceased. The court found that the stress, anxiety, and depression resulting from the negligence of Social Security led to his diabetic condition becoming uncontrolled. The court found for plaintiff.

Looking at statutory compensation schemes affords an even more direct view of how the undersigned should consider conditions unrelated to the vaccinations at issue. In Bludworth

Shipyard, Inc. v. Lira, 700 F.2d 1046 (5th Cir. 1983), the court reversed a decision of the Benefits Review Board under the Longshoremen's and Harbor Worker's Compensation Act, 300 U.S.C. §900 et seq. The Board had granted compensation to Lira who had hurt his back on the job. Lira was a former heroin addict who became re-addicted when the doctor, and subsequently the hospital which performed a back operation on him, prescribed narcotics to deaden his pain. Lira had not informed either the doctor or the hospital of his prior addiction. Although his employer Bludworth paid for all medical bills relating to Lira's back injury, it refused to pay for Lira's drug detoxification program to treat his heroin re-addiction. The United States Court of Appeals for the Seventh Circuit held that Lira's deliberate omission of the information about his prior heroin addiction was an intervening cause of his re-addiction[17] and, therefore, unlike normal compensation law, his employer would not have to pay for the detoxification. In reaching this conclusion, the Seventh Circuit discussed the doctrine of defendant's (here, employer's) taking his victim (here, employee) as he finds him.

> We have repeatedly held that an employer takes an employee as he finds him. Aggravation of a preexisting condition can be an "injury" under the Act.

Id. at 1049. The court cited numerous cases for this proposition including Hensley v. Washington Metro Area Transit Authority, 655 F.2d 264, 268 (D.C. Cir. 1981), cert. denied, 456 U.S. 904 (1982) ("[T]he fact that the injury would not have resulted but for the pre-existing disease, or might just have well been caused by a similar strain at home or at recreation, are both immaterial"); and J.V. Vozzolo, Inc. v. Britton, 377 F.2d 144, 148 (D.C. Cir. 1967) (employers accept with their employees the frailties that predispose them to bodily hurt). *Id.* at 1050, n.2.

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[17] The doctors testified that they would never have prescribed narcotics to Lira for pain relief if they had known of his prior addiction.

The court discussed the difference in legal standards under the LHWCA compared to the typical tort case (instructive for interpreting the Vaccine Act): the court's sole function was to determine whether the injury complained of arose out of the employment. This is unlike the typical tort standard of whether a party in the conduct of his everyday affairs should be held legally responsible for remote consequences of his acts: "Once the causation in fact is established, with only a few exceptions, the court's function is at an end." *Id.* at 1050. The court cited Atlantic Marine, Inc. v. Bruce, 661 F.2d 898, 901 (5th Cir. 1981) (claimant's arteriosclerosis was not a supervening cause that would prevent an award of compensation).

In citing congressional intent in passing the LHWCA, this court notices how similar that intent was to the one underlying the Vaccine Act:

> The dominant intent of Congress in enacting the LHWCA was to help longshoremen. The Act is intended to ... provide injured employees with more immediate and less expensive relief than that available in a common law tort action.

Id. at 1051.[18] The Seventh Circuit concluded that if Lira had not known of a particular weakness or susceptibility, and consequently did not know he should advise those doctors treating him of what he himself did not know, there would have been no intervening cause and Lira would have prevailed. *Id.* at 1052.

Clearly, under both common tort law (defendant takes his victim as he finds him) and statutory compensation schemes (to provide more immediate, less expensive, certain, and

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[18] Compare the language of the House Committee on Energy and Commerce pertaining to the Vaccine Act: "But for the relatively few who are injured by vaccines--through no fault of their own--the opportunities for redress and restitution are limited, time-consuming, expensive, and often unanswered." H.R. Rep. No. 908, 99th Cong., 2d Sess. 6 (1986).

generous relief), petitioners herein are entitled to damages for the effect of Madison's vaccinations (seizure disorder) whether or not the vaccinations also caused Kawasaki disease.

The undersigned can foresee that in determining damages, respondent might take the view that it is petitioners' burden to prove what proportion of Madison's damage is due to her vaccine injury (the seizure disorder) and what proportion is due to her Kawasaki disease (assuming the vaccines did not cause or significantly aggravate that as well). Respondent might also take the view that the enterovirus infection that Madison harbored subclinically until she had a runny nose and could not get rid of for a year also is a part of the physical difficulties she had and petitioners have the burden to prove what damage proportion to ascribe to the enterovirus. This is not the law.

In D'Ambra v. United States, 396 F. Supp. 1180 (D.RI 1973), aff'd, 518 F.2d 275 (1st Cir. 1975), the mother of a four-year-old boy killed by a postal truck sued the United States for her consequent psychoneurosis. The court reflected that she would not be able to recover for the psychological portion of the damage, but defendant had never presented proof as to what portion of her damage was psychological versus physical. Therefore, defendant was liable for the entire amount of her damages. In discussing the shifting of the burden of proving apportionment to defendant, the court stated:

> [W]here the negligent infliction of injury aggravates a pre-existing condition or disease, and no apportionment is possible, it has been held that the defendant is liable for the entire damage, i.e., Newbury v. Vogel, 151 Colo. 520, 379 P.2d 811 (1963) (pre-existing arthritic condition); Kawamoto v. Yasutake, 49 Hawaii 42, 410 P.2d 976 (1966) (possible prior back problems and an arthritic condition); Blaine v. Byers, 429 P.2d 397 (Idaho 1967) (pre-existing arthritic condition); Matsumoto v. Kaku, 484 P.2d 147 (Hawaii 1971) (pre-existing back pain), Wise v. Carter, 119 So.2d 40 (Fla. App. 1960) (prior injury). The justifications for this principle are, however, different from that used in the multi-collision cases. It is

> sometimes said that a tortfeasor takes his victim as he finds him. See Blaine v. Byers, supra. Another rationale is that when a prior condition does not cause pain or disability, the injury caused by the tortfeasor is the proximate cause of the pain or disability. Comment. Apportionment of Damages, 49 Denver L.J. 115, 116 (1972) and cases cited therein. See also Newbury v. Vogel, supra.

Id. at 1180.

The instant case satisfies the reasoning described in D'Ambra in that Madison did not have any seizures or seizure disorder prior to vaccination, and then developed a seizure disorder post-vaccination, and if the evidence does not permit apportionment of the damage between the prior condition (exposure to enterovirus), the subsequent condition (Kawasaki disease) and the acellular DPT and HiB vaccinations, respondent is liable for the entire damage. If evidence does permit apportionment, it is respondent's burden to provide it. The D'Ambra court continued:

> Where an injury which is indivisible is caused by the negligence of the defendant concurring with an innocent cause, as a force of nature, the defendant is held responsible for the entire injury. Haverly v. State Line & S.R. Co., 19 A. 1013 (Pa. 1890) (fire caused by negligence and wind); Jackson v. Wisconsin Tel. Co., 60 N.W. 430 (Wis 1894) (negligently left wire plus lightning); Long v. Crystal Refrigerator Co., 277 N.W. 830 (Neb. 1938) (defective building plus wind), and where an injury is theoretically divisible and one cause is innocent, the circumstance most analogous to the instant case, the aggravation of pre-existing injury cases constitute authority for holding the tortfeasor totally liable.

Id.

In Duty v. United States Dep't of Interior, 735 F.2d 1012 (6th Cir. 1984), one of the two plaintiffs in a car accident had had a pre-existing abnormal curvature of the spine at the tailbone (known as spondylolisthesis). However, she had not experienced pain from this condition prior to the accident. After the accident, she experienced substantial pain and suffering. The court held that defendant was liable for all damages proximately resulting from his negligence even

though plaintiff's injuries may have resulted from the aggravation of a pre-existing physical impairment. Id. at 1014.

See also Figueroa-Torres v. Toledo-Dávila, 232 F.3d 270, 275-76 (1st Cir. 2000) ("eggshell skull" doctrine where you take your victim as you find him is still valid; beaten prisoner who died also had enlarged spleen due to disease); Stevens v. Bangor and Aroostook Railroad Co., 97 F.3d 594, 603 (1st Cir. 1996) (Federal Employers' Liability Act or FELA has broad remedial purposes; railway worker injured in a fall had post-accident cardiac event; if the factfinder cannot separate injuries caused or exacerbated by the accident from those resulting from a pre-existing condition, defendant is liable for all such injuries).

This analysis of significant aggravation and apportionment of damages should guide petitioners and respondent as to what the requisite burdens are and who has them.

From the evidence in this case, the undersigned holds that but for the acellular DPT and HiB vaccinations, Madison would not have had seizures and a seizure disorder. That she subsequently had Kawasaki disease (which the vaccines may have been substantial factors in causing together with her enterovirus infection) and a subclinical enterovirus infection does not remove respondent's liability for compensating petitioners for all the damage to Madison which, from her subsequent MRIs, appears to come from gliosis or neuron death. Her Kawasaki disease gave her repetitive fevers, which prompted more (but not all) of Madison's seizures after her initial seizures. Respondent takes his victim as he finds her.

Dr. Tornatore's and Dr. Bellanti's testimony and respondent's articles confirm that the vaccines were substantial factors in causing her seizures and that Kawasaki disease was a substantial factor not in causing her seizures but in creating an environment that made them

occur more frequently (repetitive fevers, when she had seizures associated with fever). Her pre-existing enterovirus infection added to the sorry immune state of this unfortunate little girl, but there is no way to tease out in terms of damage the effect of the enterovirus from the effects of the vaccines or the effect of the Kawasaki disease from the effects of the vaccines.

Petitioners have made a prima facie case that acellular DPT and HiB vaccines were substantial factors in causing Madison's fever, initial seizure, seizure disorder, and subsequent developmental delay and, but for these vaccinations, she would not have the condition she has today.

CONCLUSION

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

IT IS SO ORDERED.

December 17, 2007
DATE

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