OFFICE OF SPECIAL MASTERS

No. 98-108V

(Filed: March 2, 2001)

JERRY JOSEPH TUFO and UNMI TUFO, as Parents and Next Guardians of their minor son JERRY JOSEPH TUFO, JR.,	*	
Petitioners,	*	**TO BE PUBLISHED**
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Sylvia Chin-Caplan, Boston, MA, for petitioners.
Mark W. Rogers, Washington, DC, for respondent.

DECISION

MILLMAN, Special Master

On February 11, 1998, petitioners filed a petition on behalf of their son, Jerry Joseph Tufo, Jr. (hereinafter, "Jerry"), for compensation under the National Childhood Vaccine Injury Act of 1986[1] (hereinafter the "Vaccine Act" or the "Act"). Petitioners have satisfied the requirements for a prima facie case pursuant to 42 U.S.C. § 300aa-11(c) by showing that: (1) they have not previously

[1] The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C.A. § 300aa-1 et seq. (West 1991), as amended by Title II of the Health Information, Health Promotion, and Vaccine Injury Compensation Amendments of November 26, 1991 (105 Stat. 1102). For convenience, further references will be to the relevant subsection of 42 U.S.C.A. § 300aa.

collected an award or settlement of a civil action for damages arising from the alleged vaccine injury; and (2) measles, mumps, rubella (MMR) vaccine was administered to Jerry in the United States.

Petitioners allege that MMR was a substantial factor in causing in fact Jerry's Guillain-Barre Syndrome (GBS), or, in the alternative, transverse myelitis (TM) or acute disseminated encephalomyelitis (ADEM). Respondent denies MMR caused in fact Jerry's GBS, or TM, or ADEM.

The court held a hearing in this case on October 20, 2000. Testifying for petitioners was Dr. J. Ben Renfroe. Testifying for respondent was Dr. Barry G.W. Arnason.

FACTS

Jerry was born on March 30, 1981. He received his first MMR on September 20, 1982. He received his second MMR on January 24, 1995, when he was almost fourteen years old. Eighteen days later, on February 11, 1995, he was unable to move his legs. He was evaluated at Eglin Air Force Base Hospital Emergency Room and then transferred to Sacred Heart Hospital that same day with a history of not having had a bowel movement for five to six days, and having had mild cold-like symptoms all week. Med. recs. at Ex. 8, 10.

Jerry was at Sacred Heart Hospital from February 11 to March 2, 1995. He improved slowly and had temperature spikes of 103°. On physical examination, there was no obvious source of infection. His chest x-ray was clear. On February 28, 1996, a thoracic spine MRI showed markedly abnormal appearance with mild to moderate atrophic changes from T-2 to T-6 and severe atrophy from T-6 to T-12. Med. recs. at Ex. 16, p. 1.

Written Submissions

On September 7, 1999, petitioners filed Exhibit 18, which included Tab A, a medical article describing peripheral neuropathy after rubella vaccination.[2]

On October 6, 2000, petitioners filed Exhibit 28, which consists of two medical articles and two letters published in medical journals (exhibits A through D).[3] Exhibit A discusses the cases of two children who had polyradiculoneuritis after they contracted measles. Exhibit B describes a case of a 16-month-old girl contracting GBS 10 days after receipt of MMR vaccine.

Exhibit C describes three cases of GBS following inoculation with measles/rubella vaccine in Britain during which eight million children were vaccinated. Exhibit D discusses two cases of GBS in toddlers, one week following either measles/rubella vaccine or measles vaccine. The authors noted that since GBS has occurred in association with live measles virus, it "could be expected to follow attenuated (vaccine) measles infection also."[4] They suggest that measles virus as both disease and vaccine plays an occasional role "in the pathological process which leads to demyelinization."[5]

On November 14, 2000, petitioners filed Exhibit 29, consisting of Tabs A through E, for the proposition that measles vaccine has an effect on the immunological state of the vaccinee, as shown

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[2] "Polyneuropathy Following Rubella Immunization. A Follow-Up Study and Review of the Problem," by W. Schaffner, et al., 127 *Am J Dis Child* 684-88 (1974) (Tab A).

[3] "Two Cases of Guillain-Barré Syndrome and Encephalitis after Measles," by G. Lidin-Janson, et al., 2 *Brit Med J* 572 (1972) (Ex. A); "Guillain-Barré syndrome after measles, mumps, and rubella vaccine," (letter) by K. Morris, et al., 343 *Lancet* 60 (1994) (Ex. B); "Vaccines and Guillain-Barré syndrome," (letter) by R. Hughes, et al., [ ] *Brit Med J* 1475-76 (1996) (Ex. C); and "Guillain-Barré Syndrome Following Administration of Live Measles Vaccine," by C. Grose, et al., 60 *Am J Med* 441-43 (1976) (Ex. D).

[4] 60 *Am Med J* at 442.

[5] *Id.*

by use of a tuberculin test after measles vaccination (Tab A), suppressed cutaneous delayed hypersensitivity reaction (Tab B), impaired in vitro lymphocyte response to antigen stimulation and depressed lymphocyte function (Tab C), and temporary suppression of the cellular immune system (Tabs D and E).[6]

Excerpts from the fourth article (Tab E) are instructive:

> Natural measles virus infection is well recognized for causing prolonged abnormalities in immune responses. These abnormalities include ... decreased natural killer cell activity, ... increased susceptibility to secondary infections.... Immunization with the attenuated live measles virus vaccine produces similar abnormalities in immune responses.[7]

> Alteration of immune cell function can be detected in most individuals after vaccination or revaccination with live attenuated measles virus.[8]

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[6] "Effects of Measles, Gamma-Globulin-Modified Measles and Vaccine Measles on the Tuberculin Test," by S. Starr, et al., 270 *New Eng J Med* 386-91 (1964) (Tab A); "Effect of Measles Vaccine on Immunologic Responsiveness," by P. Fireman, et al., 43 *Ped* 264-72 (1969) (Tab B); "Depressed Lymphocyte Function after Measles-Mumps-Rubella Vaccination," by T.P. Munyer, et al., 132 *J Infectious Dis* 75-78 (1975) (Tab C); "Measles Virus Vaccination of Measles Seropositive Individuals Suppresses Lymphocyte Proliferation and Chemotactic Factor Production," by R.L. Hirsch, et al., 21 *Clin Immunol & Immunopath* 341-50 (1981) (Tab D); and "Changes in Cytokine Production after Measles Virus Vaccination: Predominant Production of IL-4 Suggests Induction of a Th2 Response," by B.J. Ward, et al., 67 *Clin Immunol & Immunopath* 171-77 (1993) (Tab E).

[7] 67 *Clin Immunol & Immunopath* at 171.

[8] *Id.* at 174.

Respondent submitted 12 articles or chapters, many for the proposition of what scientific proof of causality should be.[9] Respondent's expert Dr. Arnason testified that Jerry has acute disseminating encephalomyelitis (ADEM), although petitioners alleged GBS (also known as AIDP or acute inflammatory demyelinating polyneuropathy). Of interest is that in Dr. Arnason's chapter on AIDP (R. Ex. G), he writes that the incidence of GBS following measles is "too high to be a chance occurrence," and that the frequency of measles-associated encephalomyelitis "far exceeds

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[9] Adverse Effects of Pertussis and Rubella Vaccines, Institute of Medicine (1991), pp. 197-99--on radiculoneuritis and other neuropathies, to wit, that there is insufficient evidence to indicate a causal relationship with rubella vaccine (which is German measles, not measles, vaccine) (Ex. A); Adverse Events Associated with Childhood Vaccines. Evidence Bearing on Causality, Institute of Medicine (1994), pp. 151-53--on GBS and mumps and measles vaccine, concluding that there is inadequate evidence to accept or reject a causal relationship (Ex. B); "Risk of Chronic Arthropathy Among Women After Rubella Vaccination," by P. Ray, et al., 278 *JAMA* 551-56 (1997), followed by an editorial, "Chronic Arthopathy After Rubella Vaccination in Women, False Alarm?" by P.E. Slater, 278 *JAMA* 594-95 (1997)–no increased incidence of undescribed neuropathies among women vaccinated against German measles (Ex. C); "Acute Inflammatory Demyelinating Polyradiculoneuropathy," by B.G.W. Arnason, et al., chap. 80 in Dyck's Peripheral Neuropathy, 3d ed., Vol. III (1992), pp. 1437-97–on GBS (Ex. D); Adverse Events Associated with Childhood Vaccines. Evidence Bearing on Causality, Institute of Medicine (1994), pp. 19-33 (ch. 2)–on "causality and evidence" (Ex. H); "A prospective study of acute idiopathic neuropathy. II Antecedent events," by J.B. Winer, et al., 51 *J Neurol, Neurosurgery, Psychiatry* 613-18 (1988)–on GBS (Ex. I); "Vaccine adverse events: causal or coincidental?" By R.T. Chen, et al., (comment) 351 *Lancet* 611-12 (1998)–on MMR and autism (Ex. J); Adverse Events Associated with Childhood Vaccines. Evidence Bearing on Causality, Institute of Medicine (1994), pp. 37-48–on GBS (Ex. K); "The Role of Epidemiology in Proving Individual Causation," in the Federal Judicial Center's Reference Manual on Scientific Evidence (1994), pp. 167-70–on epidemiology but notes its limitations (Ex. L); "Demyelinating Diseases Affecting the Spinal Cord," by C.M. Helgason and B.G.W. Arnason, ch. 17 of Handbook of the Spinal Cord (1987), pp. 559-606 (Ex. M); "Acute transverse myelitis: Incidence and etiologic considerations," by M. Berman, et al., 31 *Neur* 966-71 (1981) (Ex. N); and "Update: Vaccine Side Effects, Adverse Reactions, Contraindications, and Precautions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," 45 *Morbidity & Mortality Wkly Rep* RR-12 (Sept. 6, 1996), denying causation of central nervous system conditions, such as encephalopathy or encephalitis, because the incidence is below baseline, but stating that severe neurologic disorders "should be anticipated only in susceptible vaccinees" (see p. 10) (Ex. O).

that of measles-associated AIDP."[10] Dr. Arnason follows this by stating on the same page of his chapter that an association between measles and AIDP is probable. This association applies chiefly to the young, Dr. Arnason adds. He states that measles incorporates a host membrane into its coat and "[a]ll viruses tied to AIDP are, at least to some extent, neurotropic."[11] He repeats that measles is a known precipitant of acute demyelinating encephalomyelitis.

Further on in chapter 80, Dr. Arnason discusses the causation of ADEM in people vaccinated against rabies.[12] The process depended on autosensitization to central nervous system myelin basic protein (MBP). He opines that a short incubation period might be associated with severe disease.[13]

Respondent's Ex. L discusses epidemiology and states that causation is a legal, not an epidemiological, issue (p. 167), that there are other factors besides epidemiology for the factfinder to consider in ruling on causation (p. 169), and that a factfinder might find in favor of causation even when epidemiology is non-supportive (p. 170).

Respondent's Ex. M is a chapter on demyelinating diseases affecting the spinal cord, which Dr. Arnason co-authored. The authors state that their focus is on the basic pathogenic mechanisms underlying demyelination regardless of its site, which could include other areas of the central nervous system. They state, "[t]he so-called demyelinating diseases share an inflammatory

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[10] "Acute Inflammatory Demyelinating Polyradiculoneuropathy," at 1440.

[11] *Id.*

[12] *Id.* at 1443.

[13] *Id.* at 1444.

component...."[14] Subsection two of their chapter discusses perivenous encephalomyelitis (PVE), which sounds very much like, if not identical to, ADEM:

> In former times, perivenous encephalomyelitis (PVE) was most commonly encountered following vaccinations against rabies or smallpox and as a complication of acute exanthems, especially measles. ... The cause is believed to be a hypersensitivity, probably to myelin basic protein (MBP)....
>
> Rarely, necrosis of large areas of the cord may be seen in severe cases of PVE.... This reflects, in our view, the severity of the process in these instances and supports our contention...that necrosis may be a sequela of a demyelinating process. ...
>
> The lesions of PVE duplicate exactly those of acute experimental allergic encephalomyelitis. In EAE, sensitivity of T lymphocytes to MBP can be shown. Lymphocytes from acute EAE animals can be driven to proliferate in vitro by exposure to MBP. ... Antibodies to MBP were sought in the study of Lisak et al. but were not found, suggesting that the response observed was one of cell-mediated immunity.
>
> PVE most often followed the peak of the vaccination response by a few days to a week or more but occasionally preceded it. ... [N]o firm epidemiologic data are at hand at the time of writing that permit an estimation of th[e] background incidence [of PVE].
>
> Only 1 case of measles in 1000 is complicated by neurological signs and symptoms. The latent period between the rash and PVE varies from -2 to +13 days, with 90% of cases developing between +2 and +7 days. Mortality averages 20%, and half the survivors are left with residual damage. The complication is more frequent in older subjects of the exanthem, that is, those over 10 years of age....The severity of PVE bears no relationship to the severity of the measles itself, suggesting that the host rather than the infectious agent is the major determinant of the reaction. About 50% of patients with postmeasles PVE and a transverse myelitis as a component of or as the dominant clinical feature of the illness are left with residual signs.
>
> Sensitivity to MBP has been shown in measles-associated PVE (Johnson, personal communication). How or why measles might sensitize to MBP is unclear, but a possibly analogous situation has been observed in Lewis rats injected intracerebrally with a coronavirus of mice known as JHM virus. Rats infected with JHM virus develop late demyelination and concurrently develop sensitivity to MBP.

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[14] "Demyelinating Diseases Affecting the Spinal Cord," at 559.

> PVE is still encountered during or following chickenpox, and extremely rarely as a complication of rubella. PVE, although described, is very rare in mumps....
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> Since sensitivity to MBP has been reported in PVE and similar sensitivity to MBP is seen in EAE, it is perhaps germane at this point to consider EAE in somewhat more detail. Various forms of EAE have been described, and these mimic, to greater or lesser extent, several of the demyelinating syndromes that affect the spinal cord.
>
> **Acute Monophasic EAE**. The disease is usually induced by immunization with MBP in Freund's complete adjuvant (a water in mineral oil emulsion containing killed tubercle bacilli). The immune response is T-cell mediated. T-cell clones that specifically recognize MBP [are] in the lymphoid organs of all mammalian species. These clones are driven to proliferate by exposure to MBP, and after expansion, the antigen-activated T cells migrate as blasts through the circulation and across venules into the central nervous system. The T cells in the brain attract monocytes, which enter the central nervous system parenchyma, transform into macrophages, and are the final vectors of myelin destruction.
>
> Acute EAE begins abruptly 8-20 days after immunization. ... The pathologic feature is that of an acute multifocal perivenular inflammatory response with small areas of demyelination at sites of inflammatory response. Sites of predilection vary between species. In rats, for example, a transverse-myelitis-like picture is the norm. These pathologic features exactly duplicate those of PVE, as does the monophasic nature of the disease.... T cells from animals with acute EAE will adoptively transfer disease to virgin histocompatible recipients.
>
> Myelitis may be seen very rarely after administration of anti-tetanus or other types of serum.
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> Evidence indicating that PVE is an autoimmune process ... has been presented....As pointed out at some length, PVE is tied to certain infections and certain vaccinations although cases without any obvious antecedent event also occur.[15]

(References omitted.)

Respondent's Ex. N is an article on acute transverse myelitis (ATM). The authors state:

> An autoimmune cause of ATM after infection may be more likely among younger than among older individuals. Two additional patients, one under age 40 and one over age 40, developed ATM after vaccination.

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[15] *Id.* at 560-65, 585, 596.

> Several reports have mentioned the clinical and pathologic similarity among ATM, acute disseminated encephalomyelitis (ADE), and experimental allergic encephalomyelitis (EAE). EAE had been shown to be a cell-mediated, autoimmune, demyelinating disorder. Histologically, both ADE and ATM may show demyelination or necrosis. Basic myelin protein can induce allergic responses that are clinically and pathologically similar to ATM. Abramsky et al. investigated sensitivity to basic myelin protein in 10 patients with ATM. In seven, they found a definite in vitro lymphocyte transformation response to purified central nervous system myelin basic protein, and in three of eight there were sensitized lymphocytes to peripheral nerve myelin protein. Five of those with responses to central basic protein were younger than 40 and two were older than 40 years. Their results are compatible with the idea that an autoimmune mechanism explains some cases of ATM, especially in younger individuals.[16]

(References omitted.)

TESTIMONY

Dr. J. Ben Renfroe testified first for petitioners. Tr. at 4. He is a pediatric neurologist who had a fellowship in epilepsy. Tr. at 5. He has been practicing pediatric neurology for six years. *Id.* He is the director of neurophysiology at Sacred Heart Hospital and does electroencephalograms and electromyography. Tr. at 6. He has had six or seven GBS cases. *Id.* During his fellowship, he saw 20 GBS cases due to an outbreak in Houston. *Id.* He has seen five or six cases of TM. Tr. at 7. He has a large autism segment of his practice, approximately 30 to 40 children. Tr. at 8. The central and peripheral nervous systems are involved in a lot of immunologic issues dealing with autoimmune diseases. Tr. at 9.

Dr. Renfroe was Jerry's treating physician. Tr. at 10. By February 5, 1995, Jerry had been constipated for five days, which is very unusual. Tr. at 20. To Dr. Renfroe, this was Jerry's first symptom of TM, but he did not know if this preceded or was simultaneous with his GBS. *Id.* On

[16] "Acute transverse myelitis: Incidence and etiologic considerations," at 970.

February 8, 1995, Jerry twisted his ankle and went to the emergency room. *Id.* Dr. Renfroe wondered if this was Jerry's first sign of peripheral neuropathy. *Id.*

When asked about Jerry's cold-like symptoms that had lasted a week, Dr. Renfroe replied their onset was 10 days after Jerry's MMR and occurred at the same time as his bowel complaints. Tr. at 21. He thinks these were sequelae of a reaction to MMR. *Id.* Dr. Renfroe diagnosed Jerry as having GBS. Tr. at 10-11. When he initially saw Jerry, Jerry became rapidly weaker and, when his respiratory system became compromised, he needed to be intubated. Tr. at 10. Jerry had rapidly ascending neuropathy, which is classic for GBS, and areflexia. Tr. at 11. The staff discussed whether or not he had TM. *Id.* His MRI showed central lesions but Jerry's lesions were higher than the lesions associated with TM. *Id.* He had cranial paralysis. *Id.* Dr. Renfroe does not disagree with the diagnosis of GBS. Tr. at 12.

Jerry's paralysis progressed to his arms. Tr. at 14. He could not speak. *Id.* He rapidly deteriorated over one to two days. Tr. at 15. His paralysis was asymmetric, rather than complete. *Id.* He had facial diplegia and could only blink. *Id.* The neuroconduction technician said Jerry had GBS because he did not have F waves. Tr. at 16.

Jerry responded to intravenous immunoglobulin, which blocks antibodies and speeds recovery. Tr. at 17. He made a rapid turn around. Tr. at 18. His residuum is severe impairment below the waist, both sensorily and motorically. Tr. at 19. He is blocked below approximately the T-10 level because of a spinal lesion rather than GBS. *Id.*

Dr. Renfroe had two theories to explain causation from MMR: (1) the autoimmune phenomenon, or (2) immunosuppression. Tr. at 23-24. With the autoimmune theory, 10 to 12 days after receiving MMR, Jerry had autoimmune myeloradiculoneuropathy but, at the beginning of his

hospitalization, the doctors did not know of his back involvement. Tr. at 23. That did not affect their treatment of Jerry. *Id.* With the immunosuppression theory, MMR vaccine gave Jerry a transient viral syndrome. Tr. at 24. A percentage of patients are immunosuppressed after MMR. *Id.* When challenged with an unknown virus, they develop TM. *Id.* His TM may have caused his GBS because he had antibodies to both the central and peripheral nervous systems. Tr. at 24-25.

Clinically, Jerry's treatment would not have changed even if Dr. Renfroe had known of the spinal lesion. Tr. at 25-26. The clinical symptoms of Jerry's spinal lesion were his absence of bowel and bladder function resulting in his catheterization. Tr. at 26.

There are several reports of measles virus causing GBS. Tr. at 28. Measles virus incorporates host proteins in its capsule or it mimics central nervous system proteins. Tr. at 28-29.

The Joyce article in *The British Medical Journal* describes a case of TM after MMR vaccine.[17] Tr. at 32-33. There is other medical literature describing GBS after measles virus infection. Tr. at 33.

GBS is a postinfectious, autoimmune disease. Tr. at 38. TM may be autoimmune or directly infectious. *Id.* Much later, after Jerry's lower extremities failed to recover, he had an MRI which discovered that he has TM. Tr. at 39. Dr. Renfroe opined that MMR was the cause. Tr. at 39-40. His basis is that Jerry's clinical course creates a plausible and probable association that he had an immunosuppressive or autoimmune response based on Dr. Renfroe's clinical experience, his knowing Jerry, and the medical literature. Tr. at 40. He thought there could be a combination of

[17] Petitioners did not submit the Joyce article into evidence.

immunosuppressive responses because GBS can be a feature of HIV. Tr. at 41. Many proteins and glycolipids are similar in the central and peripheral nervous systems. Tr. at 45.

There is a temporal relationship to these challenges to Jerry's immunological defenses. Tr. at 50. It takes over a week to have immune suppression after MMR. Tr. at 51. An opportunistic virus could have appeared 10 days post-MMR. *Id.*

On cross-examination, Dr. Renfroe stated that Jerry's mild cold-like symptoms could not have caused his GBS because they were simultaneous with the GBS's onset. Tr. at 55-56. But, the upper respiratory syndrome could have been a viral syndrome, which is a frequent reaction 10 days after an MMR inoculation. Tr. at 56.

Jerry had an elevated protein in his cerebrospinal fluid above 300 (the normal range is zero to 50). Tr. at 58. His white cells were 62, consistent with an ongoing infection and inflammatory process. Tr. at 59-60. He thinks that the MMR caused both a viral infection whose onset was February 3, 1995, and Jerry's GBS and TM whose onset was February 10, 1995. Tr. at 63- 66. MMR is a live, attenuated virus vaccine. Tr. at 73. Viruses are strongly associated with GBS. *Id.* Jerry's GBS began 17 days after vaccination, on February 10, 1995. Tr. at 103–4.

In his clinical experience, if GBS follows MMR by two weeks and there is no other known antecedent, it is biologically plausible, temporally-related, and supported by the medical literature that the vaccine caused it. Tr. at 145-46.

Dr. Barry G.W. Arnason testified for respondent. Tr. at 186. He is a professor of neurology at the University of Chicago and has treated 150 GBS cases. Tr. at 186-87. His opinion is that Jerry did not have GBS. Tr. at 187. Jerry had a central nervous system disease, a destructive myelopathy involving his thoracic cord. *Id.* It acutely evolved from his lower extremities to his upper

extremities, and compromised his cranial nerves and breathing. *Id.* It happened over 12 hours, just one day. Tr. at 187-88. This is a highly unusual course for GBS. Tr. at 188. Jerry's white cell count of 62 on spinal tap was high for GBS. *Id.* His protein was elevated to 368, but one does not see elevation until two to five days elapse in GBS. *Id.*

Jerry had sensory loss below the T-6 level with bowel and bladder incontinence. *Id.* His bladder incontinence persists. *Id.* Areflexia is expected in acute transverse myelitis because the spinal cord is utterly destroyed in the lower spine. Tr. at 189. Jerry had a necrotizing myelopathy, causing extensive destruction, which is the same as transverse myelitis. *Id.*

His EMG was consistent with GBS because of the absent F waves. Tr. at 189-90. But the nerve impulse cannot go through if the nerve is destroyed. Tr. at 190. There is no evidence for GBS in this case. *Id.* Dr. Arnason's opinion is that Jerry had ADEM. *Id.* Cold symptoms are a common cause of ADEM. Tr. at 191. Billions of people receive MMR. Tr. at 192. The number of cases of neurological complications is vanishingly small. *Id.* One in 10,000 people get ADEM. *Id.* Dr. Arnason believes that Jerry's cold caused his ADEM. Tr. at 199-200. The reason is that infectious illness more often causes ADEM than vaccinations. Tr. at 200. Jerry's white blood cell count was 15,000, suggesting an infectious process. Tr. at 203.

However, the timing was right for MMR and an infection, and it is biologically plausible that MMR caused Jerry's infection and that MMR caused his ADEM. Tr. at 205-06. Measles is associated with delayed-type hypersensitivity responses. Tr. at 206. It worsens tuberculosis. *Id.* It is a failure of the immune system. Tr. at 207. It can also be associated with ADEM. *Id.* Delayed-type hyperactivity is turned on in ADEM (a T-cell response). *Id.* In ADEM, the response is directed against myelin basic protein. *Id.*

Measles vaccine can cause abnormalities of lymphocyte function in the test tube and a loss of reactivity in the immune system. Tr. at 209. Processes are directed toward other antigens. *Id.* Certain infections, such as mycoplasma, dispose a person to ADEM. Tr. at 213.

Dr. Arnason does not know how to explain Jerry's five to six days of bowel dysfunction at the time of his cold symptoms. He found nothing in the literature and it is outside his experience. Tr. at 215-16.

Dr. Arnason has treated 15 cases of ADEM over 30 years. Tr. at 216-17. He does not see children that often. Tr. at 217. In children with ADEM, 50 percent have a preexisting infectious illness. *Id.* Dr. Arnason treats adults, but ADEM is more common in children because they have more infections and more vaccinations. Tr. at 217-18.

Dr. Arnason is comfortable with the diagnosis of ADEM in Jerry because of his brainstem symptoms and weakness in his upper spinal cord. Tr. at 222-23. The most common cause of ADEM is measles. Tr. at 223. Two-thirds of the cases of ADEM are due to measles. Tr. at 224. It occurs once in 1,000 people. Tr. at 223. ADEM was the reason for developing the measles vaccine. *Id.* It could be a rare complication of the vaccine. Tr. at 224. Since the administration of measles vaccination, we now have one-third the number cases of ADEM we used to have. Tr. at 224.

Dr. Arnason thinks it highly unlikely that MMR is the cause of Jerry's ADEM. Tr. at 228. The most common cause of ADEM is infectious illness. Tr. at 229.

GBS is a steady movement upwards, but Jerry's course bounced from place to place. Tr. at 232-33. Measles virus can cause GBS, but there is no evidence that measles vaccine causes GBS although it is biologically plausible. Tr. at 233-34. Myelin basic protein is in both the central and peripheral nervous systems. Tr. at 236-37. ADEM curiously does not involve the peripheral nervous

system. Tr. at 237. It may, however, involve sensitivity to additional proteins than myelin basic protein. *Id.* The lesions of ADEM involve dissemination in space, but not in time. Tr. at 238. It is a monophasic disease with no recurrence. *Id.* Jerry had a very severe form of ADEM. *Id.* He is left with transverse myelitis. Tr. at 239. No MRI was done on Jerry's cervical spine or brain. Tr. at 240.

Measles is a potent immunosuppressor. Tr. at 247. It is well-known that measles virus reactivates tuberculosis. *Id.* It would not surprise Dr. Arnason if measles vaccine is an immunosuppressor. Tr. at 248. There is no data to suggest that a vaccinee has an increased risk of respiratory infection. Tr. at 249. Opportunistic infections can occur with immunosuppression, but Dr. Arnason would not relate that to measles vaccine. Tr. at 250. To accept causation, Dr. Arnason would like to have animal models, to know the protein structures of wild measles and measles vaccine and the relative immunogenicity of the two, and to see excess cases of ADEM among measles vaccinees compared to the background rate. Tr. at 253-54.

DISCUSSION

Petitioners are proceeding on a theory of causation in fact. To satisfy their burden of proving causation in fact, petitioners must offer "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury. A reputable medical or scientific explanation must support this logical sequence of cause and effect." Grant v. Secretary, HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Agarwsal v. Secretary, HHS, 33 Fed. Cl. 482, 487 (1995); see also Knudsen v. Secretary, HHS, 35 F.3d 543, 548 (Fed. Cir. 1994); Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993).

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, supra, 956 F.2d at 1149.

Petitioners must not only show that but for the MMR vaccine Jerry would not have had the injury, but also that the vaccine was a substantial factor in bringing about his injury. Shyface v. Secretary, HHS, 165 F.3d 1344 (Fed. Cir. 1999).

In essence, the special master is looking for a reputable medical explanation of a logical sequence of cause and effect (Grant, supra, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, supra, 35 F.3d at 548-49). To the undersigned, medical probability means biologic credibility or plausibility rather than an 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, [99th Cong., 2d Sess. 18, *reprinted* in 1986 U.S.C.C.A.N. 6344], 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.

Although the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), listed various criteria for federal district court judges to follow in their role as gatekeeper for the admission of scientific and medical evidence, such criteria are merely aides in evaluation, rather than prescriptions, for the Office of Special Masters. Even in federal district courts, "Daubert's list of specific factors neither necessarily nor exclusively applies . . . in every case

. . . [and its] list of factors was meant to be helpful, not definitive." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 141, 151 (1999).

In the Office of Special Masters, the Federal Rules of Evidence are not required.[18] Invariably, consistent with the legislative intent in creating the Vaccine Program, the special masters admit most evidence. But see, Domeny v. Secretary, HHS, No. 94-1086V, 1999 WL 199059 (Fed. Cl. Spec. Mstr. March 15, 1999), aff'd, (Fed. Cl. May 25, 1999) (unpublished), aff'd, No. 99-5130 (Fed. Cir. Apr. 11, 2000) (rejecting proffer of dentist's testimony for diagnosis of a neuropathy).

As the Federal Circuit stated in Knudsen, supra, 35 F.3d at 548, "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules." Thus, the task before the undersigned is not to delineate how petitioners' evidence does or does not satisfy the Daubert litany of support in peer-reviewed medical literature, concurrence among a majority of physicians in the field of immunology and/or neurology, and confirmative testing of methodology. Rather, the task is to determine medical probability based on the evidence before the undersigned in this particular case.

The evidence in this case is very much a battle of the experts. Dr. Renfroe, Jerry's treating pediatric neurologist, opined that Jerry's MMR vaccination was the immunological challenge that produced his GBS two and one-half weeks later, which left him with transverse myelitis. Timing is crucial in understanding the nature of an immune-mediated disease. The medical literature is supportive of Dr. Renfroe's explanation that Jerry's illness was immune-mediated. The medical

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[18] CFC Rules, Vaccine Rule 8(b) Evidence. "In receiving evidence, the special master will not be bound by common law or statutory rules of evidence. The special master will consider all relevant, reliable evidence, governed by principles of fundamental fairness to both parties."

articles in evidence are replete with discussions of both measles and measles vaccine being immunosuppressors. Animal studies are also supportive of measles inducing reactions against myelin basic protein and causing a neurological disease, experimental allergic encephalomyelitis (EAE), that is analogous to human acute disseminated encephalomyelitis (ADEM).

Dr. Arnason testified for respondent that Jerry has ADEM, and the court finds his testimony as to the diagnosis of Jerry's disease more credible than Dr. Renfroe's diagnosis. Dr. Arnason has vastly more experience in diagnosing and treating GBS patients than does Dr. Renfroe, and Dr. Arnason has written medical chapters on both AIDP (also called GBS) and PVE (which is similar if not identical to ADEM). The rapidity of Jerry's symptoms, and the magnitude of his central nervous system involvement, rule out his having a peripheral nervous system disease.

Although Dr. Arnason thinks that Jerry's cold-like symptoms caused his ADEM, he does not place any medical significance on Jerry's bowel dysfunction, which occurred at the same time as his cold symptoms. Dr. Renfroe opined that Jerry's bowel dysfunction was the beginning of his transverse myelitis, and the court finds his opinion more credible than Dr. Arnason's which attributes no medical significance to the bowel dysfunction. Since the beginning of Jerry's central nervous system problem was simultaneous with his cold, the cold could not have caused it. There would not have been enough time for immunosuppression. The court also finds credible Dr. Renfroe's testimony that MMR can cause nasal congestion 12 or 13 days later. The court holds that the MMR caused both Jerry's cold-like symptoms and the onset of his ADEM within 12 or 13 days of vaccination.[19]

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[19] The undersigned has previously held that tetanus vaccine caused ADEM in a young girl. Johnson v. Secretary, HHS, No. 99-219V, 2000 WL 1141582 (Fed. Cl. Spec. Mstr. Jul. 27, 2000).

Dr. Arnason admitted that this is a biologically plausible sequence of events for a causative relationship. Dr. Renfroe, although he adhered to the GBS diagnosis, opined that this is the proper timing to cause an immune-mediated illness. What is striking to the court is that the most common cause of ADEM is the measles virus, and the vaccine at issue is a live (though attenuated) measles virus vaccine. The medical literature reiterates and the court discussed that the severity of the reaction is unrelated to the strength of the virus. Thus, that the virus is attenuated in the vaccine does not make it less likely than the natural or wild virus to be the cause of ADEM.

Dr. Arnason testified that cases of ADEM have diminished to one-third of their prior number because measles vaccination was instituted and the most common cause of ADEM is measles. Once people are vaccinated, they do not contract measles as a general rule and, therefore, are less likely to contract ADEM. But Dr. Arnason admitted it is biologically plausible that measles vaccine causes ADEM.

Rare events, such as transverse myelitis in Herkert,[20] acute hemolytic anemia in Brown,[21] and ADEM in Johnson, have not appeared in epidemiological studies pertaining to vaccination so far, yet petitioners have prevailed in those cases. The Federal Circuit in Knudsen, supra, did not find lack of epidemiological support an impediment to petitioners' prevailing. In Knudsen, even though epidemiological evidence supported the opposite conclusion, i.e., that viruses were more likely to cause encephalopathy than vaccinations, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

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[20] Herkert v. Secretary, HHS, No. 97-518V, 2000 WL 141263 (Fed. Cl. Spec. Mstr. Jan. 19, 2000).

[21] Brown v. Secretary, HHS, No. 99-044V, 2000 WL 1207255 (Fed. Cl. Spec. Mstr. Aug. 3, 2000).

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

So too, in this case, although more individuals contract ADEM from wild measles or other infections than from measles vaccine, that alone does not impede petitioners from recovering damages. Studies of experimental allergic encephalomyelitis (EAE) show reactivity against myelin basic protein (MBP) in animals. Dr. Arnason has written that measles-associated perivenous encephalomyelitis shows hypersensitivity to MBP. In vitro (in glass) testing described in the literature shows immune reactivity to central nervous system MBP among patients with acute transverse myelitis. The literature that both parties filed shows that ADEM is an immune-mediated response, and that it has a corollary in both animal and in vitro testing.

The timing here is appropriate for an immune-mediated response. The pathological process described in the medical literature is consistent with what happened to Jerry clinically. The only ingredient missing is epidemiologic support, and the Federal Circuit has held that it is not essential, and even when epidemiology leads a conclusion opposite to vaccine causation, petitioners may still prevail when a condition is rare. ADEM is unquestionably rare. As respondent's exhibit L discusses, causation is a legal, not an epidemiological, issue, and the factfinder may find in favor of causation even when epidemiology is non-supportive.

All the undersigned must do, under the holdings of the Federal Circuit in Grant and Knudsen, is find a logical sequence of cause and effect to rule for petitioners. Both experts agreed that measles virus is a significant immunosuppressor, and that measles vaccine causing ADEM is biologically

plausible. The medical literature submitted includes cases of ADEM following vaccination. The court finds Dr. Renfroe more credible than Dr. Arnason in evaluating the immunologic issues, medical literature, and factors in Jerry's case in reaching his conclusion that MMR caused Jerry's illness, even though Dr. Arnason's diagnosis of the illness as ADEM was more credible than Dr. Renfroe's diagnosis of GBS. As for causation, Dr. Arnason would admit only that it is biologically plausible.

Petitioners have satisfied their burden of showing a logical sequence of cause and effect between MMR vaccine and Jerry's ADEM based on: (1) the testimony of Dr. Renfroe, Jerry's treating pediatric neurologist, (2) the medical literature which supports that vaccinations are a known cause of ADEM; (3) the understanding of immune-mediated disease, particularly those manifesting hypersensitivity to MBP; (4) the time sequence here which was appropriate for an immune-mediated response; and (5) the simultaneous occurrence of cold-like symptoms and bowel dysfunction, which means that the former could not have caused the latter due to the lack of time for an immune-mediated response to occur.

CONCLUSION

Petitioners are entitled to reasonable compensation. The undersigned hopes that the parties may reach an amicable settlement, and will convene a telephonic status conference soon to discuss the filing of life care plans, unless the parties agree on a joint life care plan. The parties should be aware that alternate dispute resolution is available to them as well, and if they choose ADR, they should contact the undersigned. Should the parties not be able to settle this case, the undersigned will hold a damages hearing.

IT IS SO ORDERED.

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DATE Laura D. Millman
Special Master