OFFICE OF SPECIAL MASTERS

No. 01-357V

(Filed: October 1, 2003)

EMMA HART, as Representative of the Estate of MANASSEH MICLEA, Deceased, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	**TO BE PUBLISHED**

__Richard Gage, Cheyenne, Wyoming, for petitioner.__

__Traci R. Manning, Department of Justice, Washington, D.C., for respondent.__

DECISION

HASTINGS, ***Special Master.***

This is an action seeking an award under the National Vaccine Injury Compensation Program[1] (hereinafter "the Program") on account of the death of the petitioner's son, Manasseh Miclea. For the reasons stated below, I conclude that petitioner is not entitled to such an award.

I

BACKGROUND FACTS AND PROCEDURAL HISTORY

Manasseh Miclea was born to the petitioner on January 1, 1998, and generally appeared to be healthy though his first year of life. On April 10, 1999, at age 15 months, Manasseh received

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[1]The applicable statutory provisions defining the Program are found at 42 U.S.C. § 300aa-10 *et seq*. (2000 ed.). Hereinafter, all "§" references will be to 42 U.S.C. (2000 ed.).

several vaccinations, including an "MMR" (measles, mumps, rubella) immunization. (Ex. 4[2], pp. 9, 12.[3]) During the next several days, Manasseh's mother apparently made one or two telephone calls to the pediatrician's office to report that Manasseh was not feeling well and had a rash. (Ex. 4, p. 12.) On April 22, 1999, he was brought to the pediatrician's office, where it was recorded that he had been feverish for the past two days, then developed a rash that day. (Ex. 4, pp. 9, 12.) In the following days, Manasseh developed more symptoms of illness. His parents apparently made several calls to the pediatrician's office, and he was taken into the office on both May 2 and May 5, 1999, with symptoms including fever, crying, vomiting, red throat, rash, and swollen red gums. (Ex. 4, p. 13.) More symptoms and physician visits took place on May 6, 7, 8, and 9. (Ex. 4, pp. 14-15.) Manasseh was hospitalized from May 9 through 20, 1999, then readmitted on May 21, as his condition deteriorated. A number of physicians were consulted, but Manasseh's condition grew worse, and he was eventually found to be suffering from a rare condition known as "hemophagocytic lymphohistiocytosis," or "HLH." He died on June 20, 1999. The death certificate listed the immediate cause of death as "general organ failure," due to conditions including "lymphohistiocytosis." (Ex. 5.) Listed as a condition contributing to death was "epstein barr viral infection." (*Id*.) No autopsy was performed.

On June 14, 2001, the petitioner filed this Program proceeding, contending that Manasseh's death was caused by his vaccinations of April 10, 1999. Respondent contested petitioner's claim, and considerable evidence was introduced in documentary form. An evidentiary hearing was held on November 8, 2002, at which hearing was taken the testimony of three expert witnesses, to be discussed below. Posthearing briefs were filed thereafter, the last of which was filed on April 28, 2003. After reviewing the record, I requested additional clarification of the expert opinions, which was provided at a hearing held on September 2, 2003.

II

STATUTORY BACKGROUND

Under the Program, compensation awards are made to individuals who have suffered injuries after receiving certain vaccines listed in the statute. There are two separate means of establishing entitlement to compensation. First, if an injury specified in the "Vaccine Injury Table," originally

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[2]Petitioner filed exhibits 1 through 5 on August 6, 2001, and additional consecutively numbered exhibits on several occasions thereafter. Respondent has filed a number of exhibits designated as Exhibit A, Exhibit B, etc. "Ex." references will be to those exhibits. "1-Tr." references will be to the pages of the transcript of the hearing held on November 8, 2002. "2-Tr." references will be to the pages of the transcript of the hearing held on September 2, 2003. (I note that in the transcript of the second hearing, the reporter repeated mistakenly transcribed references to the "EB" virus as "BE.")

[3]Pages 9 and 12 of Exhibit 4 seem to both constitute the same page of the records of Manasseh's pediatrician, but page 12 contains additional notations not on page 9, apparently notations of phone calls to the pediatrician's office.

established by statute at § 300aa-14(a) and since modified administratively, occurred within the time period from vaccination prescribed in that Table, then that injury may be *presumed* to qualify for compensation. § 300aa-13(a)(1)(A); § 300aa-11(c)(1)(C)(i); § 300aa-14(a). If a person qualifies under this presumption, he or she is said to have suffered a "Table Injury." Alternatively, compensation may also be awarded for injuries not listed in the Table, but entitlement in such cases is dependent upon proof that the vaccine "actually caused"--*i.e.*, "caused-in-fact"-- the injury. § 300aa-13(a)(1); § 300aa-11(c)(1)(C)(ii).

The vaccinations that Manasseh received on April 10, 1999, are covered under the Program. In this case, the petition originally alleged that Manasseh suffered unspecified Table Injuries. By the time of the hearing in this case, however, petitioner had abandoned any Table Injury theory, and argued solely that Manasseh's death was "caused-in-fact" by the MMR (measles, mumps, rubella) vaccination that Manasseh received on April 10, 1999.

Therefore, the dispute to be resolved here concerns only whether petitioner has demonstrated that it is "more probable than not" that Manasseh's death was "caused-in-fact" by his MMR vaccination administered on April 10, 1999.

III

RESOLUTION OF "CAUSATION-IN-FACT" ISSUE

A. The required showing

In analyzing a contention of "causation-in-fact," also known as "actual causation," the presumptions available under the Vaccine Injury Table are, of course, inoperative. It is clear that the burden is on the petitioner to show that in fact the vaccination in question more likely than not caused the injury or death. *See, e.g., Hines v. Secretary of HHS*, 940 F.2d 1518, 1525 (Fed. Cir. 1991); *Carter v. Secretary of HHS*, 21 Cl. Ct. 651, 654 (1990); *Strother v. Secretary of HHS*, 21 Cl. Ct. 365, 369-70 (1990), *aff'd* 950 F.2d 731 (Fed. Cir. 1991); *Shaw v. Secretary of HHS*, 18 Cl. Ct. 646, 650-51 (1989). Thus, the petitioner must supply "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." *Shaw*, 18 Cl. Ct. at 651; *Hasler v. United States*, 718 F.2d 202, 205-06 (6th Cir. 1983), *cert. denied* 469 U.S. 817 (1984); *Novak v. United States*, 865 F.2d 718, 724 (6th Cir. 1989). The petitioner need not show that the vaccination was the sole cause or even the predominant cause of the injury or death, but must demonstrate that the vaccination was at least a "substantial factor" in causing the injury or death, and was a "but for" cause. *Shyface v. Secretary of HHS*, 165 F. 3d 1344, 1352 (Fed. Cir. 1999).

I conclude that petitioner has not met her burden of demonstrating that it is "more probable than not"[4] that the vaccination caused Manasseh's HLH or his death. My reasoning will follow.

B. Analysis of the evidence in this case

1. The issue: What "triggered" the HLH?

In this tragic case concerning the death of Manasseh Miclea, it is clear that, as agreed by the experts who testified in this proceeding, Manasseh died as a result of a condition known as "hemophagocytic lymphohistiocytosis," or "HLH." HLH is a rare, and usually fatal, disease of infancy. The disease is not fully understood, but appears to result from a defective, overacting operation of the victim's immune system. The two principal experts in this case--Dr. Melvin Berger for respondent and Dr. Vera Byers for petitioner[5]--agree that, as shown by the medical literature filed by both parties in this case, cases of HLH seem to be "triggered" by some stimulus such as infection. Most commonly that stimulus has been determined to be a virus, but the trigger apparently can be a non-viral infection such as a bacterial infection, or some other agent such as a cancer.[6]

Accordingly, both parties agree that the issue in this case is *what stimulus* triggered Manasseh's tragic case of HLH. Dr. Byers opined that it was likely the MMR vaccination that Manasseh received on April 10, 1999. Dr. Berger, on the other hand, finds it most probable that the Epstein-Barr virus was the trigger of Manasseh's disease.

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[4]Petitioner has the burden of demonstrating the facts necessary for establishing entitlement to an award by a "preponderance of the evidence." § 300aa-13(a)(1)(A). Under that standard, the existence of a fact must be shown to be "more probable than not." *In re Winship*, 397 U.S. 358, 371 (1970) (Harland, J., concurring).

[5]Dr. Berger is a physician who is board-certified in the specialties of pediatrics and allergy/immunology. (1-Tr. 124-126; Ex. B.) Dr. Byers is a physician who is board-certified in internal medicine and also experienced in the areas of allergy/immunology and medical toxicology. (1-Tr. 22-23; Ex. 9.)

[6]Medical scientists have often divided HLH into two categories. In some instances HLH seems to recur in families, and it is suspected that there is a genetic problem that makes individuals in these families susceptible to HLH. In such cases, the condition is often described as "familial hemophagocytic lymphohistiocytosis," or "FHL." (Ex. 10.) In cases of HLH where there does not seem to be a familial recurrence, the condition is sometimes described as "virus-associated hemophagocytic syndrome," or "VAHS." (Ex. 11.) However, according to the record in this case it appears to be generally agreed that in *both* categories of cases, including FHL, there is likely some kind of agent that "triggers" the condition. Thus, for purposes of this case it seems to make no difference whether Manasseh's case fits into one or the other of those two categories.

2. The experts' respective theories

Dr. Byers notes that viruses are apparently the most common triggers of HLH, and that the MMR vaccination contains live, though weakened (*i.e.*, "attenuated"), versions of the measles, mumps, and rubella viruses. She notes that the medical record made on April 22, 1999, indicates that Manasseh had developed a fever two days beforehand and a rash on that day (Ex. 4, p. 9), which symptoms in her view likely constituted a reaction to the measles vaccine.[7] Dr. Byers opines that the fact that the measles vaccine affected Manasseh enough to cause the rash and fever means that such vaccine was likely the trigger of the HLH, which had its onset only a couple of weeks later. Dr. Byers also discounts the possibility that the trigger was Epstein-Barr virus, as Dr. Berger argues. She argues that the tests that indicated the existence of Epstein-Barr virus in Manasseh were either "false positives" or the product of unproven, unreliable tests.

Dr. Berger, on the other hand, relies chiefly on the facts that (1) the Epstein-Barr virus is by far the most common trigger of HLH, and (2) two different tests on Manasseh during his HLH ordeal indicated that the child was infected with the Epstein-Barr virus. Dr. Berger finds it far more likely that the Epstein-Barr virus was the HLH trigger than the possibility that one of the attenuated viruses in the MMR vaccine was the trigger.

3. Analysis

After careful consideration, I find that petitioner has failed to carry her burden of demonstrating that it is "more probable than not" that Manasseh's HLH was vaccine-caused. The shortest summary of my reasoning is that I found Dr. Berger's argument to be more persuasive than that of Dr. Byers and petitioner's other expert witness, Dr. Stanton. Another very brief summary is that while it seems *possible* that the MMR vaccination triggered Manasseh's HLH, that possibility certainly does *not* seem *more likely* than the possibility that the Epstein-Barr virus was the trigger. A more detailed summary of my reasoning is contained in the following five paragraphs.

Initially, I note that the argument of Dr. Byers and Dr. Stanton has at least some appeal; there certainly seems to be at least some possibility that the MMR vaccination was the trigger. As indicated above, the literature indicates that different types of viruses or even non-viral agents can trigger HLH. Therefore, it seems at least theoretically possible that an "attenuated" virus, such as those contained in the MMR vaccine, could be a trigger. Further, Dr. Byers pointed to two cases in which persons suffered hemophagocytic syndromes after infection by the "wild" measles virus[8]

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[7]Fever and rash are common reactions to measles vaccine, and usually appear one to two weeks post-vaccination. Indeed, Manasseh's treating pediatrician wrote on April 22, 1999, that the symptoms likely constituted either a "viral exanthem" (*i.e.*, rash due to a virus) or an "MMR reaction." (Ex. 4, p. 9.)

[8]The term "wild" refers to a virus in its ordinary, natural form, as opposed to the "attenuated" version of the virus used in a vaccine.

(Exs. 13 and 16); one case in which a person suffered a hemophagocytic syndrome after infection by the wild rubella virus (Ex. 15); and one case in which an infant suffered hemophagocytic histiocytosis after receiving the MMR *vaccine*, after which the treating physicians apparently concluded that the vaccination triggered the disease (Ex. 14). These cases offer some support to Dr. Byers' theory that the viruses contained in the MMR inoculation, in either their wild or vaccine forms, may be capable of triggering HLH. And the fact that Manasseh did suffer a rash and fever about 10-12 days after his MMR vaccination, in the time frame typical for similar reactions to the measles or rubella vaccinations, also adds some weight to the possibility that the MMR vaccination could have been the HLH trigger. Indeed, based upon the HLH literature and the expert testimony contained in the record of this case, if there were no indication that Manasseh was infected by the Epstein-Barr virus, then I likely *would* conclude that Manasseh's HLH was probably triggered by one of his vaccinations received on April 10, 1999.

The problem for petitioner, however, is that, as Dr. Berger stresses, Manasseh's medical records also contain evidence that he was infected by the *Epstein-Barr virus*, which is by far the most common cause of HLH. In light of that evidence, as Dr. Berger argues, it does not seem reasonable to conclude that the MMR vaccination was a *more likely* trigger than the Epstein-Barr virus.

First, I note that the medical literature introduced by both parties, along with the testimony of the experts, indicates that one particular virus, the Epstein-Barr virus, also known as the "EB virus" or "EBV," has been identified as by far the most common trigger for HLH. Dr. Byers acknowledged that, as Dr. Berger indicated, Epstein-Barr virus has been the most commonly identified trigger. (1-Tr. 104.) Dr. Byers seemed to estimate that, based upon her review of the literature, in about 50% of HLH cases Epstein-Barr virus is identified as the trigger.[9] (1-Tr. 47.) One article submitted by petitioner reviewed 219 cases and found the Epstein-Barr virus to be the trigger in 121 cases (55 %), with another virus identified as the trigger in 28 cases, non-viral triggers identified in 14 cases, and no trigger identified in 56 cases. (Ex. 11, p. 437.) Dr. Berger also looked at other literature regarding HLH triggers, and found that the Epstein-Barr virus was implicated as the trigger in 18% to 95% of the cases involved in each article. (Ex. C, p. 3.)

Second, the evidence in this case, to be discussed in detail below, makes it seem quite probable that in May of 1999 Manasseh was suffering from an active infection of the Epstein-Barr virus.

Putting these two facts together, I am persuaded that, as Dr. Berger (and several of Manasseh's own treating physicians) reasoned, it is quite probable that the trigger of Manasseh's HLH was the Epstein-Barr virus. While it is *possible* that the MMR vaccination was the trigger, that possibility seems to be substantially less likely than the possibility that the Epstein-Barr virus was the trigger.

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[9]At another point, Dr. Byers estimated that in about 50% of the cases no trigger is found. (1-Tr. 104.)

I will elaborate on my reasoning in the several sections below.

a. The evidence indicates that Manasseh likely was infected by Epstein-Barr virus

In response to Dr. Berger's view that the Epstein-Barr virus was the most likely trigger of Manasseh's HLH, Dr. Byers' chief argument was an attempt to discredit the evidence of Epstein-Barr infection in Manasseh. This is obviously an extremely important issue.

I start by noting that two different tests indicated that Manasseh was infected by the Epstein-Barr virus. First, on May 10, 1999, a test was performed on Manasseh's bone marrow, and the results were interpreted by the testing laboratory as "suggesting that this patient has been exposed to EBV [Epstein-Barr virus]." (Ex. 7, p. 542.) Later, on June 8, 1999, a "PCR" test of Manasseh's blood also indicated the presence of Epstein-Barr infection. (Ex. 7, p. 233 (bottom of page); Ex. 7, p. 4.[10]) Dr. Berger bases his conclusions chiefly on those two tests.

Dr. Byers attacked those two tests as unreliable. Concerning both tests, she noted that the particular tests utilized had not been approved by the U.S. Food and Drug Administration (FDA). (1-Tr. 26-29.) With respect to the bone-marrow test, she also stressed that the test report stated that positive cells were "scattered" throughout the sample (Ex. 7, p. 542), which Dr. Byers did not find to be sufficient to call it a "positive" test (1-Tr. 62-63). She noted that the test report itself seemed to equivocate concerning how strong the positive result was, stating that "this analysis is difficult to interpret * * *, and the specificity of the result in this setting is not well-established yet." (Ex. 7, p. 542.) In addition, Dr. Byers pointed to two additional tests, the antibody tests, which did *not* indicate that Manasseh had been exposed to Epstein-Barr virus. (1-Tr. 83.)

Dr. Berger, however, defended the reliability of the two tests that indicated Epstein-Barr infection, testifying that he would rely upon them. (1-Tr. 126-27, 129-31.) He explained in detail why he believes that the bone-marrow test should be viewed as a positive result. (1-Tr. 145-147.) Dr. Berger testified that the antibody test results should not negate the findings of the two positive tests. (1-Tr. 129-30, 134-36, 138-40, 148-151.) Moreover, he stressed that it was extremely unlikely that two different types of tests would by chance both yield a positive finding of Epstein-Barr infection. (1-Tr. 129-130.)

This is a difficult issue, but, after full consideration, I conclude that Manasseh likely did suffer an infection by the Epstein-Barr virus.

First, I did not find much merit in Dr. Byers' argument that both the blood and bone-marrow tests should be disregarded because they were not FDA-approved tests. Dr. Byers did not explain

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[10]At Ex. 7, p. 4, the note, likely a transcription of a physician's oral dictation, states that "An EVPCR of Manasseh's blood was done which was positive * * *." This clearly indicates that an "EB [Epstein-Barr] PCR" test was done.

the FDA approval process for these types of tests, nor did she explain whether it is common or routine for these types of tests to go through the FDA approval process. She did not give me any context for evaluating whether a lack of FDA-approval for these tests is any reason to discount them. To the contrary, the record in this case does not provide any substantial evidence indicating that I should discount these tests. Dr. Berger explained that the absence of FDA approval is simply because the FDA does not regulate these types of tests. (2-Tr. 63; Ex. H, p. 1; Ex. H-1, p. 1.) He testified that these types of testing are commonly utilized and relied upon by treating physicians. (2-Tr. 64-66.) Further, Dr. Byers herself acknowledged that based upon those two tests, if she had been Manasseh's treating physician she would have relied upon those tests, at least insofar as administering to Manasseh a drug known as acyclovir, a non-toxic treatment for Epstein-Barr virus. (1-Tr. 47-48, 64.) Dr. Byers also acknowledged that it was common practice for physicians to rely upon laboratory tests that are not FDA-approved. (1-Tr. 102, lines 19-22.) Finally, and very importantly, it appears that Manasseh's *treating physicians* did believe that these tests were reliable, since those physicians ordered such tests, treated Manasseh with the drug acyclovir as a result of those tests, and indicated in the medical records the belief that such tests indicated that Manasseh had suffered Epstein-Barr infection. For example, Dr. Sarah Fryberger, a hematologist, wrote that Manasseh had suffered "epstein-barr viral infection." (Ex. 5.) Dr. Scott Lindquist, an infectious disease specialist, wrote that the bone-marrow test was "positive for EBV." (Ex. 3, p. 32.) And Dr. Alex Kitzis, a resident physician at the hospital, noted that the PCR blood test for Epstein-Barr "was positive as was the bone marrow for EPV [obviously meaning "EBV"] that had been done previously." (Ex. 7, p. 4.)

Accordingly, I cannot find it appropriate to disregard the above-described test results simply because the tests were not FDA-approved.

Second, I have carefully considered Dr. Byers' comments concerning whether the result of the *bone-marrow test* (also described as the "EBER" test in the transcript) should really be considered a "positive" result. I conclude that despite Dr. Byers' concerns, the result should be considered as "positively" indicating that Manasseh had been infected by Epstein-Barr virus.

Dr. Byers seemed to rely upon the fact that the test report indicated positive cells "scattered throughout" the bone-marrow sample, and she questioned whether this scattering was enough to indicate infection. (1-Tr. 62-63.) But, in response, Dr. Berger pointed to studies of HLH victims in which the percentage of positive cells identified in similar tests seemed to be consistent with the "scattered throughout" language of the test report (1-Tr. 145-47), and Dr. Byers did not thereafter rebut that testimony of Dr. Berger.[11] Further, while the author of the test report wrote that the test was "difficult to interpret" and that the "specificity of the result * * * is not well-established yet," nevertheless that author concluded that the test "suggest[s] that this patient has been exposed to EBV [*i.e.*, Epstein-Barr virus]." (Ex. 7, p. 542.) And, again very significant in my view, Manasseh's

[11]To the contrary, upon cross-examination, Dr. Byers admitted that she did not know exactly what percentage of positive cells would be sufficient to constitute a "positive" result for Epstein-Barr exposure on this type of test. (1-Tr. 114.)

treating physicians seem clearly to have interpreted the bone-marrow test as positively indicating exposure to Epstein-Barr virus. As noted above, Dr. Fryberger wrote that Manasseh had suffered "epstein-barr viral infection" (Ex. 5); Dr. Lindquist wrote that the bone-marrow test was "positive for EBV" (Ex. 3, p. 32); and Dr. Kitzis noted that the PCR blood test for Epstein-Barr "was positive as was the bone marrow [test] for [Epstein-Barr virus] that had been done previously" (Ex. 7, p. 4).

Accordingly, having considered Dr. Byers' difficulties with the bone-marrow test and the caveats set forth in the test report itself, I nevertheless find the bone-marrow test to be a significant piece of evidence showing it to be quite likely, if not certain, that Manasseh was infected with Epstein-Barr virus.

Third, I have also carefully considered the results of two sets of tests, performed on May 10 and June 8, 1999, which indicated that Manasseh's immune system was *not manufacturing antibodies* to the Epstein-Barr virus. (See Ex. 7, pp. 232-33.) As Dr. Byers pointed out, such test results would, by themselves, seem to indicate that Manasseh had *not* been infected with the Epstein-Barr virus. Dr. Byers argued that the negative results of these two tests should be interpreted as indicating that the other two, above-described tests were false positives, and that Manasseh was never exposed to Epstein-Barr virus. (1-Tr. 31-32, 36; Ex. 8, p. 4.)

Dr. Berger, however, explained that in some cases persons infected with Epstein-Barr virus do not make antibodies to that virus. Dr. Berger testified that while it would be "uncommon" for a person to show no antibody response to Epstein-Barr virus while having a positive PCR blood test for Epstein-Barr, it would *not* be "highly unusual." (1-Tr. 134.) He pointed to one study, cited by Dr. Byers and filed by petitioner, in which 32 persons suffering from HLH were determined to have had Epstein-Barr virus as the trigger for the HLH, yet in three of those 32 persons serology testing did *not* show an antibody response to Epstein-Barr virus. (Ex. 12, p. 2, Table 2, "EBV-specific serology"; 1-Tr. 129-30; 134-137.) He also pointed to a study in which several persons died of illnesses similar to HLH thought to have been caused by Epstein-Barr virus, yet serologic testing of several of those persons did not reveal an antibody response to Epstein-Barr virus. (1-Tr. 148-151, Ex. E.[12]) Dr. Berger opined that Manasseh was likely an example of those individuals cited in those two studies who, for some reason, were infected by the Epstein-Barr virus but did not make antibodies to the virus. (1-Tr. 151.)

This is a difficult point. The fact that the two antibody tests were negative, of course, certainly makes me pause before concluding that Manasseh probably was infected by the Epstein-Barr virus. As Dr. Byers has pointed out, Manasseh's immune system at some point was able to make antibodies to other viruses. (1-Tr. 31-32.) Dr. Berger, however, has made an effective point by citing the studies, noted above, in which in some victims the Epstein-Barr virus was determined

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[12]On October 11, 2002, respondent filed four medical articles. The cover sheet properly described these as respondent's Exhibits D through G (respondent had previously filed Exhibits A, B, and C), but inadvertently the exhibits were tabbed as A, B, C, and D. When I cite to "Ex. E," I refer to the article by Martinez and colleagues designated as Ex. E but mistakenly tabbed as "B".

to have caused HLH or related disorders, yet the patients showed no antibodies to Epstein-Barr virus. Further, Dr. Berger has explained *why* that could happen; he explained that in a small number of persons, certain cells may be infected with the Epstein-Barr virus, yet there is a failure of other cells to "recognize" that such infection has occurred, so that no antibodies to that virus are manufactured. (2-Tr. 74-78.) Petitioners' experts did not effectively refute that explanation.

Considering all the evidence, I conclude that Manasseh likely *was* infected by Epstein-Barr virus, despite the lack of antibody response in the two tests, for three major reasons. First, and most importantly, *two* separate tests, the bone-marrow test and the PCR blood test, showed infection, making it seem quite unlikely that two different types of tests on two different types of body tissue would both yield "false positives." Second, as Dr. Berger has shown by pointing to the studies cited above, it appears that some victims of HLH and similar disorders caused by Epstein-Barr virus do not make antibodies to the virus. Third, certain of Manasseh's *treating physicians* concluded, despite knowledge of the negative antibody tests, that Manasseh likely was exposed to Epstein-Barr virus. That is, as noted above, Dr. Fryberger wrote that Manasseh had suffered "epstein-barr viral infection" (Ex. 5); Dr. Lindquist wrote that the bone-marrow test was "positive for EBV" and that such virus was therefore the "most likely" trigger[13] for the HLH (Ex. 3, p. 32); and Dr. Kitzis noted that both the PCR blood test and the bone-marrow test were positive for Epstein-Barr exposure, and that the HLH was "likely triggered" by the Epstein-Barr virus (Ex. 7, p. 4).

b. The tests support the presence of an active, not past, infection in May 1999

Petitioner has argued that the PCR blood test performed on June 8, 1999, showed only that Manasseh had been exposed to the Epstein-Barr virus *at some time* in the past, not necessarily an infection recent enough to trigger the HLH. That is true, but, of course, the PCR test does not indicate whether the infection was in the distant past or not. The June 8 test could also mean that Manasseh was *currently* suffering from Epstein-Barr infection or had been exposed in the very recent past.

Further, the bone-marrow test performed on May 10, 1999, did indicate a *current, active* infection--*i.e.*, it indicated that the Epstein-Barr virus was actively replicating in Manasseh's body at that time. (1-Tr. 138.)

Accordingly, I conclude that the two tests, taken together, indicate that it is quite probable that Manasseh was suffering from an *active* Epstein-Barr infection in May of 1999.

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[13]Dr. Lindquist wrote that "the most likely virus on my differential is Epstein-Barr virus." "Differential" is short for "differential diagnosis," and the clause as a whole clearly means that Dr. Lindquist viewed Epstein-Barr virus as the most likely trigger for HLH.

c. Other issues respecting Epstein-Barr virus

In addition to attacking the reliability of the bone-marrow test and PCR blood test as discussed above, petitioner has also raised other issues with respect to whether Manasseh was likely infected with Epstein-Barr virus. Petitioner argues that Manasseh was the "not a typical age" to be infected by that virus; had no known exposure to another person with that virus; and had no clinical symptoms of Epstein-Barr infection. (See Pet. Post-Trial Memorandum filed on Feb. 26, 2003, pp. 18-21.)

As to the age issue, petitioner points to testimony of Dr. Byers and Dr. Stanton to the effect that the most common age for experiencing "infectious mononucleosis" is age 15 to 25. (1-Tr. 41, 71.) However, Dr. Berger explained that while the Epstein-Barr virus does cause infectious mononucleosis, it also causes other conditions, especially in younger children. (1-Tr. 128, 140-141.) He explained that approximately 50% of children have experienced Epstein-Barr infection by age 10. (1-Tr. 128.)

As to the exposure issue, while it is true that no one can say exactly from whom Manasseh might have gotten the virus, that is likely true with respect to many infections. Dr. Stanton, Manasseh's treating pediatrician who appeared in this proceeding as a witness for petitioner, seemed to acknowledge that Manasseh might have picked up a virus in the pediatrician's waiting room or somewhere else. (1-Tr. 87--"he was in our waiting room, goodness knows where else he was, could he have picked up a viral illness[?] * * * sure.") Moreover, the two tests discussed above simply indicate that Manasseh did pick up the virus *somewhere*--which Dr. Berger said happens to 50% of children by age 10--even if we don't know where.

As to the issue of clinical symptoms, petitioner argues that it is impossible to point to particular clinical symptoms of Manasseh and say that they constitute clinical symptoms of an Epstein-Barr infection. Petitioner makes much of the fact that in his written report in this case Dr. Berger seemed to indicate the view that Manasseh likely suffered an "initial vaccine-induced" reaction of feverishness and rash on April 22, "followed by a second infection" in early May "which triggered the fatal response" (*i.e.*, the HLH). (Ex. C, p. 1.) Petitioner points to testimony at the hearing indicating that the early May symptoms were actually symptoms of the HLH, not of a second infection. Petitioner argues that Dr. Berger at the first evidentiary hearing seemed to back off from his above-quoted statement at Ex. C, p. 1, that a "second infection" in early May likely triggered the HLH. Note that at the first hearing Dr. Berger seemed to agree with Dr. Stanton that the early May symptoms were caused by the HLH, rather than constituting symptoms of a second infection. (1-Tr. 155-156.) The question is whether that apparent concession by Dr. Berger at the first hearing undermines his entire theory of the case, as petitioner seems to argue. I do not find that it does.

First, at the second hearing, Dr. Berger clarified his opinion concerning the symptoms in early May; while he agreed that *some* of Manasseh's symptoms in early May were HLH symptoms, he argued that certain of the May symptoms were classic symptoms of HLH. (2-Tr. 67-71, 82-90, 103.) I found that testimony to be logical and persuasive, well-supported by Dr. Berger's references

to a standard medical text, and I found Dr. Byers' brief effort to respond to that testimony (2-Tr. 91-92) to be unpersuasive. On the basis of the record in this case, I find that the symptoms displayed by Manasseh on or around May 9, 1999, upon which Dr. Berger relies, likely (through not certainly) were symptoms of Epstein-Barr infection.

Moreover, an even more important point is that Dr. Berger's theory of this case is based primarily on the *two laboratory tests* discussed above, rather than on any clinical symptoms, as proof that Manasseh experienced Epstein-Barr infection. And I am persuaded by Dr. Berger's logic that these laboratory tests are convincing evidence that Manasseh did experience active Epstein-Barr infection in May of 1999. That is true even though we cannot say with *certainty* whether any of Manasseh's many symptoms in May constituted clinical symptoms of Epstein-Barr infection rather than a reaction to HLH symptoms. Some of those symptoms may in fact have been symptoms of an Epstein-Barr infection, or maybe none were. Even in the latter event, the *laboratory test results* are enough to persuade me that Manasseh likely did experience Epstein-Barr infection.

d. Issue of "attenuated" viruses vs. Epstein-Barr virus

Another point that supports my ultimate conclusion, in at least a minor way, is the fact that the versions of the measles, mumps, and rubella viruses contained in the MMR vaccine are "attenuated" viruses--*i.e.*, they are intentionally weakened so that they will not have ill effects on the vaccinee. Dr. Berger pointed out that one aspect of this attenuation process in these vaccines is that the attenuation is designed to reduce the amount of "cytokines" that the vaccination provokes in the vaccinee's immune system. (1-Tr. 133, 144.) And it is undisputed that HLH is triggered by cytokines. (1-Tr. 37, 155.) Therefore, while the MMR's attenuated viruses *in theory* could trigger HLH (Dr. Berger acknowledged that he knew of no quantified minimum amount of cytokines necessary to trigger HLH--1-Tr. 161), the fact that these attenuated viruses are designed to produce fewer cytokines seems to support Dr. Berger's theory that the MMR viruses are *less* likely to have triggered the HLH than the Epstein-Barr virus.

e. Opinions of treating physicians

It is significant that Dr. Stanton, one of the two physicians offered by petitioner as expert witnesses in this case, was Manasseh's actual treating pediatrician. I have always welcomed and paid careful attention to the testimony of treating physicians in Program cases. Such witnesses, of course, have the special advantage that it seems less likely that they would have the inherent bias of an expert witness retained for litigation purposes. I certainly appreciate greatly Dr. Stanton's willingness to provide his opinion in detail in this case. Thus, it adds considerable weight to petitioner's case that Dr. Stanton has been willing to opine that the MMR vaccination was the likely cause of Manasseh's HLH.

However, weighing against this opinion of Dr. Stanton are the opinions of *other* of Manasseh's treating physicians--*i.e.*, the specialists who treated Manasseh in the hospital during his illness. First, the physician listed as Manasseh's "attending physician" at the hospital (see Ex. 7,

p. 4), Dr. Fryberger, seems to have concluded that the Epstein-Barr virus was the likely trigger of the HLH, since she wrote on the death certificate that "epstein-barr viral infection" was a "condition contributing to death." (Ex. 5.) In addition, Dr. Lindquist, an infectious disease specialist who consulted on Manasseh's case, wrote that the Epstein-Barr virus was the "most likely" trigger for the HLH. (Ex. 3, p. 32--see fn. 13 above.) And Dr. Kitzis, a resident physician who authored the hospital's "expiration summary" after Manasseh's death, dictated that "it was felt that" the HLH "was likely triggered by EPV," obviously referring to the Epstein-Barr virus. (Ex. 7, p. 4.)

Accordingly, although I have carefully considered Dr. Stanton's opinion, I have also considered the opinions of the other treating physicians contained in the medical records, which support Dr. Berger's view of the case. On balance, I conclude that these opinions, as a whole, add as much or more weight to Dr. Berger's view as to Dr. Byers'.

f. The Knudsen issue

Another argument raised by petitioner in one of her post-hearing memorandums is the contention that--

> respondent's statistical argument that "EBV has been reported as the trigger for HLH more often than other viruses" is, as a matter of law, not evidence and not relevant in the Vaccine Program.

(See Pet. Reply Memorandum filed April 28, 2003, p. 5.) Petitioner cites *Knudsen v. Secretary of DHHS*, 35 F.3d 543, 550 (Fed. Cir. 1994), as the basis for this argument. I have considered this contention, but find it to be without merit.

Petitioner apparently bases this argument upon the following passage from the *Knudsen* opinion:

> 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 555. Petitioner seems to argue that as a matter of law, in considering a factual question concerning "causation" of a condition, a Program factfinder may not consider statistical evidence concerning the relative frequency of causes of a particular condition.

I conclude that petitioner's argument is incorrect. The above-quoted sentence from the *Knudsen* opinion must be considered in context. In *Knudsen*, it was undisputed that the injured vaccinee had suffered an "encephalopathy," in such circumstances that the injury qualified as a "Table Injury," *presumed* to be caused by a DPT vaccination under the Program scheme. (See discussion of the "Table Injury" concept at pp. 2-3 above.) The only issue was whether the

respondent had carried the *respondent's burden* of demonstrating that the vaccinee's encephalopathy was nevertheless noncompensable because it was proven to be "due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(B). In that context, the court of appeals concluded that it would be improper to find that *a particular vaccinee's* encephalopathy was due to a viral infection *merely* on the basis of statistical proof that, *in general*, viral encephalopathies are more common than vaccine-caused encephalopathies. The court of appeals ruled that there must be some specific evidence in the case at hand showing it to be probable that the *particular vaccinee's* encephalopathy was caused by a viral infection. And that ruling of *Knudsen* makes sense, because otherwise in *every* "Table Injury encephalopathy" case involving a DPT vaccination, the respondent could simply rely on statistical evidence that other types of encephalopathies are more frequent than DPT-caused encephalopathies, and therefore the encephalopathy "Table Injury" would become a nullity.

In this case, in contrast, there is no allegation by petitioner of a Table Injury. This is, instead, a case in which petitioner alleges "causation-in-fact." It is, thus, the *petitioner's* burden to show that it is "more probable than not" that Manasseh's HLH was triggered by a vaccination. The above-described holding in *Knudsen* is therefore irrelevant to this case.

Moreover, it simply seems untenable to argue, as petitioner apparently does here, that *Knudsen* stands for the startling proposition that *no* "statistical evidence" of *any* kind can *ever* be considered in analyzing a factual issue in a Program case. The fact is, of course, that statistical evidence is very often relevant in deciding scientific questions. The *Knudsen* court should not be deemed to have endorsed the dubious proposition that in resolving factual questions involving scientific issues, a whole category of extremely relevant evidence must always be ignored.

Accordingly, I conclude that the approach that I have used in analyzing the evidence concerning the Epstein-Barr virus in this case is not contrary to the *Knudsen* decision.

g. The Ackley and Gall decisions

Finally, petitioner notes that in two previous Program cases, special masters found that vaccinations triggered cases of HLH. In *Gall v. Secretary of HHS*, No. 91-1642V, 1999 WL 1179611 (Fed. Cl. Spec. Mstr. Oct. 31, 1999), Special Master Edwards concluded that an infant's case of HLH (described as "FHL"--see footnote 6 above) was likely triggered by DPT and/or OPV vaccinations. In *Ackley v. Secretary of HHS*, No. 98-122V, 2002 WL 985435 (Fed. Cl. Spec. Mstr. April 29, 2002), Special Master Abell found that the vaccinee's case of HLH was likely triggered by an MMR inoculation.

I have closely read and considered those two opinions, but they do not change the result that I reach in this case. The key point is that in neither of those opinions was there an indication that either of the HLH victims had tested positive for the Epstein-Barr virus, or any other potential triggering agent other than the vaccinations in question. That makes those two situations far different from the situation here, where two tests did indicate Epstein-Barr infection. Thus, I do not

believe that the result that I have reached in this case is inconsistent in any way with the *Gall* and *Ackley* decisions.

h. Summary

In sum, the evidence of record in this case indicates that while the MMR vaccination was a *possible* trigger of Manasseh's HLH, it is more likely that an infection by the Epstein-Barr virus was the trigger. That is so chiefly because the Epstein-Barr virus is recognized as by far the most common trigger of HLH, and because testing on Manasseh indicated that he was infected by the Epstein-Barr virus at the time of his fatal illness. Accordingly, I conclude that petitioner has failed to carry her burden of demonstrating that it is "more probable than not" that Manasseh's HLH and death were vaccine-caused.

IV

CONCLUSION

The story of the short life of Manasseh Miclea is a tragic one. His mother, the petitioner, is deserving of great sympathy for her grievous loss. Congress, however, designated the Program to compensate only the families of individuals whose injuries or deaths can be linked causally, either by evidence or by Table Injury presumption, to a listed vaccination. In this case, as described above, no such link has been demonstrated. Accordingly, the petitioner in this case is not entitled to a Program award.[14]

_____

George L. Hastings, Jr.
Special Master

[14]In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.