IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS
No. 01-190V
Filed: May 29, 2009
To Be Published

THOMAS D. HENNESSEY,	*	
	*	Omnibus Proceeding,
Petitioner,	*	Type 1 Diabetes, Juvenile
	*	Diabetes, Insulin Dependent
v.	*	Diabetes Mellitus, Hepatitis
	*	B Vaccine, Causation,
SECRETARY OF THE DEPARTMENT	*	Evaluating Expert Opinions,
OF HEALTH AND HUMAN SERVICES,	*	Autoimmune Disease,
	*	Weight of the Evidence,
Respondent.	*	Alternative Cause,
	*	Significant Aggravation

Sylvia Chin-Caplin, Esq. of Conway, Homer, Chin-Caplan, P.C., Boston, MA, for petitioner.
Nathaniel McGovern, Esq., (hearing) and *Daryl Wishard, Esq*. (onbrief), United States Department of Justice, Washington, D.C. for respondent.

DECISION[1]

Vowell, Special Master:

On April 2, 2001, Ms. Gwen Hennessey ["Ms. Hennessey"] timely filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"], on behalf of her minor son,

[1] Because I have designated this decision to be published, petitioner has 14 days to request redaction of any material "that includes medical files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire decision will be publicly available. 42 U.S.C. § 300aa12(d)(4)(B).

[2] Part 2, National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa.

Thomas D. Hennessey[3] ["petitioner" or "Mr. Hennessey"], alleging that he was injured by the hepatitis B vaccination he received on September 15, 1998. The petition did not specify the injury received, but the medical records accompanying it indicated that Mr. Hennessey was diagnosed with juvenile diabetes, also known as Type 1 diabetes ["T1D"],[4] on November 30, 1998, and that his mother attributed his diabetes to vaccination. Petitioner's Exhibit ["Pet. Ex."] 4, p. 3-4. Although no expert report was filed with the petition, subsequent filings established that Mr. Hennessey's T1D is the injury claimed. *See* Petitioner's Post-Hearing Brief ["Pet. Post-Hearing Br."] at 1-2 ("The [hepatitis B] vaccines...were a substantial contributing factor, and but for the vaccines, he would not have suffered IDDM."). Although it was not initially clear whether Mr. Hennessey was proceeding on a causation or a significant aggravation claim, it now appears that he was alleging that the hepatitis B vaccines caused an aggravation or acceleration of an underlying pre-diabetic condition.

To be eligible for compensation under the Vaccine Act, a petitioner must either demonstrate a Vaccine Table[5] injury, to which a statutory presumption of causation attaches, or prove by a preponderance of the evidence that a vaccine listed on the Vaccine Table caused or significantly aggravated an injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Grant v. Sec'y, HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Mr. Hennessey does not contend that he suffered a "Table" injury. Because he is proceeding under a significant aggravation theory, he must demonstrate that the vaccines caused a "change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). Causation is demonstrated by application of the three *Althen* factors. Therefore, in order to prevail, he must demonstrate 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,* 418 F.3d at 1278. *See also Hines v. Sec'y, HHS*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

As reflected in the discussion below, there are at least two theoretical bases for the contention that vaccines can play a role in causing T1D. The first is that vaccines

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[3] On March 31, 2006, I granted a motion to recaption this case, as Mr. Hennessey had reached the age of majority.

[4] Type 1 diabetes is variously referred to as juvenile diabetes, autoimmune diabetes, and insulin dependent diabetes mellitus ["IDDM"], or simply diabetes mellitus. Except when quoting a medical record, article, or expert opinion, I will refer to Mr. Hennessey's condition as T1D. Further information concerning this disease and its diagnosis, treatment, and postulated causes is provided, *infra.*

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

induce the initial (and generally slow) autoimmune attack on the pancreatic β islet cells.[6] The second is that, in an individual already experiencing the slow destruction of the β islet cells, a vaccine accelerates the process, pushing the individual into clinically overt T1D. While theoretically plausible, the overwhelming weight of the evidence is to the contrary with regard to either theory.

Based on the record as a whole,[7] I conclude that petitioner has failed to establish by preponderant evidence that any vaccine he received either caused or significantly aggravated his condition. I thus deny Mr. Hennessey's petition for compensation.[8]

I. Procedural History.

Because this case is the "test case" for an omnibus proceeding,[9] I set forth the procedural history in some detail. Before turning to that procedural history, I address

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[6] In the hearing transcript, expert reports, and supporting scientific articles, these cells are sometimes referred to as "beta cells" or "B islet" cells. They should not be confused with B lymphocytes, the white blood cells that are part of the adaptive immune system .

[7] *See* § 300aa–13(a): "Compensation shall be awarded...if the special master or court finds on the record as a whole..." *See also* § 300aa–13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation).

[8] Based on the causation evidence developed in this omnibus proceeding, appropriate orders will be issued in the other T1D cases pending before the court. Unlike multi-district litigation in federal district courts, the outcome of this case does not dictate the outcome in the other cases that are a part of this omnibus proceeding, but the evidence developed may be applied to those cases.

[9] The Vaccine Act contains no specific provisions for omnibus proceedings, which bear some resemblance to multi-district litigation in federal district courts. *See* 28 U.S.C § 1407. However, the Act permits the consideration of evidence without regard to formal rules of evidence. Certain provisions of the Vaccine Act and its legislative history indicate that Congress contemplated that the special masters would develop expertise in the complex medical and scientific issues involved in actual causation claims and would apply the expertise they developed in the course of resolving cases to other cases. *See, e.g.*, H.R. Conf. Rep. 101-386, 1989 WL 168141 (November 21, 1989) (Conference Report on the 1989 amendments stated: "The system is intended to allow the proceedings to be conducted in what has come to be known as an 'inquisitorial' format, with the master conducting discovery (as needed), cross-examination (as needed) and investigation."). *See also Hodges v. Sec'y, HHS*, 9 F.3d 958, 961 (Fed. Cir. 1993) ("Congress assigned to a group of specialists, the Special Masters within the Court of Federal Claims, the unenviable job of sorting through these painful cases and, based upon their accumulated expertise in the field, judging the merits of individual claims."). Although due process concerns preclude the wholesale importation of evidence adduced in one proceeding to another proceeding without the consent of the parties, in omnibus proceedings, the parties consent to import evidence from the "test case" into other individual cases. Absent such consent, special masters generally advise the parties when they intend to consider evidence derived from their own efforts, usually in the form of medical journal articles, and permit the parties to comment on such evidence. Institute of Medicine ["IOM"] Reports, learned treatises, medical textbooks, medical dictionaries, or handbooks explaining medical abbreviations or tests are often consulted and referenced in the body of an opinion without formal notice to the parties. *See, e.g.*, *Stroud v. Sec'y, HHS*, 113 F.3d 1258 (Fed. Cir. 1997) (special masters may rely upon an IOM report that neither party filed as evidence).

the use of omnibus proceedings in Vaccine Act cases.

A. Omnibus Proceedings.

Recognizing that cases involving the same vaccine and injury often involve the same body of medical expertise, the Office of Special Masters ["OSM"] developed the concept of omnibus proceedings to answer the common question of whether a particular vaccine can cause the injury in question–the general causation question. The issue of whether it did so in a specific case can then be resolved more expeditiously, based on a ruling in an omnibus test case.[10]

At least two types of omnibus proceedings have been developed. The first involves applying evidence developed in the context of one or more individual cases to other cases involving the same vaccine and the same or similar injury. *See, e.g., Capizzano v. Sec'y, HHS*, 440 F.3d 1317 (Fed. Cir. 2006). The second involves hearing evidence on a general theory of causation, making findings based on that evidence, and ordering the parties to file matters establishing the extent to which the facts of individual cases fit within the framework developed. *See, e.g., Ahern v. Sec'y, HHS*, No. 90-1435V, 1993 U.S. Claims LEXIS 51 (Fed. Cl. Spec. Mstr. Jan. 11, 1993).

In the rubella arthropathy proceeding detailed in *Ahern*, Special Master Hastings used the second type of omnibus proceeding. He considered evidence developed on the general issue of whether the rubella vaccine could cause chronic arthritis or other joint problems. The general causation evidence was developed in a proceeding in which two counsel representing a large number of petitioners and counsel for respondent filed expert reports and medical journal articles. Special Master Hastings then conducted a hearing in which the medical experts testified. He published an order setting forth the conclusions he had reached from the evidence presented, and filed it into each of the rubella arthropathy cases. Concluding that there was sufficient evidence that the rubella vaccination could cause chronic arthropathy under specified conditions, he indicated that individual petitioners would be entitled to compensation if they met all of those conditions. He then ordered additional filings by each petitioner to establish whether they met those criteria. *Ahern*, 1993 U.S. Claims LEXIS 51, *46-55. *See also Snyder v. Sec'y, HHS*, No. 94-58V, 2002 U.S. Claims LEXIS 371, *62-66 (Fed. Cl. Spec. Mstr. Dec. 15, 2002).

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[10] For example, the common issue of whether Vaccine A can cause Disease X might be heard in the context of an individual case. If the special master determines that Disease X could, indeed, be caused by Vaccine A, the special master would also attempt to determine under what circumstances causation could be established, what specific symptoms would be required, and when those symptoms must manifest in order to attribute the disease or injury to the vaccine. The findings, issued in the context of deciding an individual case, would then provide guidance to the parties in other cases involving that vaccine and injury. Such findings might result in settlement or withdrawal of many pending cases without the necessity of additional hearings. Omnibus proceedings have resolved claims that the polio vaccine caused polio, that the rubella vaccine caused some arthritic conditions, and that the hepatitis B vaccine caused various demyelinating conditions.

Most omnibus proceedings, however, have involved hearing evidence and issuing an opinion in the context of a specific case or cases. Then, by the agreement of the parties, the evidence adduced in the omnibus proceeding is applied to other cases, along with any additional evidence adduced in those particular cases. Thus, the parties are not bound by the results in the test case, only agreeing that the expert opinions and evidence forming the basis for those opinions could be considered in additional cases presenting the same theory of causation.

Both methods have proven efficient in resolving similar cases, when, based on the special master's analysis of the scientific evidence, the parties opt to settle or dismiss the remaining claims. However, the first method has the disadvantage that the special master's findings amount to an advisory opinion. Using the first type of omnibus proceeding might well delay final resolution of affected cases, as either party might contest application of the evidence developed, but have no case ripe for appeal until the general causation evidence is applied to a particular case.

B. Genesis of the T1D Omnibus Hearing.

The T1D omnibus proceeding involved the second method, hearing general causation evidence in the context of a test case. Mr. Hennessey's petition was one of several hundred petitions filed after the hepatitis B vaccine was added to the Vaccine Injury Table in 1997,[11] alleging that the hepatitis B vaccine caused a wide spectrum of injuries. This large number of petitions placed a measure of strain on both the bench and bar,[12] and so, in an effort to more efficiently handle the caseload involving claims of injury from the hepatitis B vaccine, Chief Special Master Golkiewicz, in coordination with counsel for petitioners and respondent, developed several case groupings and methods for processing what became known as the "Hep B" cases. In this case, as in most other hepatitis B cases filed during this period, petitioner was not prepared to produce evidence of vaccine causation at the time the petition for compensation was filed, and thus informally sought a stay of the proceedings. Petitioner's case was therefore stayed "until petitioner notifies this court that petitioner is prepared to proceed." Order, dated February 24, 2003 (a joint order issued in this and numerous other cases).

On September 26, 2003, a special master issued a decision in a T1D case, denying compensation. *See Baker v. Sec'y, HHS*, No. 99-653V, 2003 U.S. Claims LEXIS 290 (Fed. Cl. Spec. Mstr. Sep. 26, 2003). Although the *Baker* decision had no

[11] The Vaccine Injury Table, 42 C.F.R. § 100.3, lists the vaccines covered by the Vaccine Act. Hepatitis B vaccine was added to the Vaccine Injury Table as of August 6, 1997.

[12] *See* Order, dated June 21, 2001, indicating that petitioner's counsel in this case had approximately 80 cases alleging injury from the hepatitis B vaccine pending before the court at that time.

precedential value for any other case,[13] it was indicative of that special master's reasoning and her assessment of the lack of evidentiary support for vaccine causation of T1D. She then issued orders in other T1D cases assigned to her, referencing the evidence developed in *Baker*. That evidence demonstrated that the time period between the onset of the disease process in T1D and the onset of observable symptoms was a lengthy one. Noting that, in most of those cases, the time frame between the allegedly-causal vaccination and onset of T1D symptoms was relatively short, the special master ordered petitioners to show cause why their cases should not be dismissed.[14]

In his response to the special master's show cause order (*see* n. 14), petitioner's counsel indicated that he had found a "credible expert who was expected to offer an opinion on vaccine causation"[15] that would challenge the evidence developed in *Baker.* Petitioner's counsel also indicated that he believed the general evidentiary issues in "all pending diabetes cases should be tried together." *Alsheimer* Pet. Reply to Show Cause Order at 10. The special master accepted counsel's assertions that he had located an expert, and gave him until March 17, 2004, to file an opinion on causation. The special master concluded the order with a direction "to advise the undersigned whether petitioner's expert will be part of an omnibus proceeding to decide all of counsel's diabetes type 1 cases assigned to the undersigned." *Alsheimer* Order, dated January 7, 2004. On March 19, 2004, petitioner's counsel filed a belated motion for additional time "to file an expert opinion and/or a report to the special master about the status of the investigation." *Alsheimer* Petitioner's Motion for Additional Time ["Pet. Motion Add'l Time"], dated March 19, 2004, at 1-2. Although this motion pertained specifically to the *Alsheimer* case, once again, petitioner's counsel referenced Mr. Hennessey's petition (Pet. Motion Add'l Time, n. 2), and discussed the issue of vaccine causation of T1D in terms of general as well as specific causation. The special master granted the requested extension.

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[13] The decisions of the Court of Appeals for the Federal Circuit are binding on special masters. *Guillory v. Sec'y, HHS*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 Fed. Appx. 712 (Fed. Cir. 2004). Decisions issued by special masters and judges of the Court of Federal Claims constitute persuasive, but not binding, authority. *Hanlon v. Sec'y, HHS*, 40 Fed. Cl. 625, 630 (1998).

[14] No show cause order was issued in Mr. Hennessey's case. However, the response of his counsel to the October 24, 2003, show cause order issued in *Alsheimer v. Sec'y, HHS*, No. 03-1708V included a reference to Mr. Hennessey's case. *See* Petitioner's Reply to Special Master's Order to Show Cause ["Pet. Reply to Show Cause Order"], filed December 23, 2003, at 10, n. 10. For all practical purposes, it appeared that the T1D cases filed by this attorney were being treated as a group.

[15] The response to the show cause order also challenged the applicability of *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 578 (1993) to the Vaccine Program. Pet. Reply to Show Cause Order at 8-10. However, petitioner did not challenge the applicability of *Daubert* to a special master's analysis of evidence in his post-hearing submissions. The Federal Circuit has approved a special master's use of *Daubert's* factors to analyze the weight to be given evidence in Vaccine Act cases. *Terran v. Sec'y, HHS*, 41 Fed. Cl. 330, 336 (1998), *aff'd,* 195 F.3d 1302, 1316 (Fed. Cir. 1999), *cert. denied, Terran v. Shalala*, 531 U.S. 812 (2000).

In May, 2004, petitioner's counsel requested an additional sixty day extension in the *Alsheimer* case, noting that he was exploring several additional theories of causation based on the advice of the initial expert he had consulted. Pet. Motion Add'l Time at 2-3 and n.1 (filed in the *Alsheimer* case). He also noted the Chief Special Master's efforts to obtain a review by an independent panel of experts at the National Academies of Science regarding allegations of injuries from the hepatitis B vaccine. *Id*. at 3. The special master granted the requested extension. *Alsheimer* Order, dated June 1, 2004.

On August 2, 2004, petitioner's counsel filed a status report and a motion to transfer his T1D cases. Although filed into the *Alsheimer* case, counsel requested transfer of eight cases, including Mr. Hennessey's case, into a "mercury toxicity" group of cases (referring to one group of "Hep B" cases), asserting that, as "the preservative thimerosal, containing ethylmercury, may play a role in causation, it is requested that all hepatitis B/diabetes cases be transferred to the 'mercury toxicity' grouping of cases."[16] *Id.* at 6.

In response to this request, on August 31, 2004, the special master suspended all further action in Mr. Hennessey's case, and in those of seven other petitioners who alleged vaccines had caused their T1D, pending the outcome of discovery in the Omnibus Autism Proceeding ["OAP"]. *See* Petitioner's Pre-Hearing Submission ["Pet. Pre-Hearing Sub."] at 1 (noting the suspension of proceedings pending the outcome of discovery in the OAP). The connection between the T1D cases and the OAP discovery process concerned the role, if any, played by mercury compounds in vaccines in the development of autism and the expected applicability of that evidence to other diseases.

This case and the other T1D cases remained stayed until reassigned to me on February 8, 2006. The discovery period in the OAP having concluded, I scheduled this case for a joint recorded status conference on March 24, 2006. At that status conference, petitioner's counsel indicated that his theory of causation in his T1D cases (which had grown to 16[17]) involved the thimerosal component of the vaccines, rather

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[16] Thimerosal is a preservative used in vaccines packaged in multi-dose vials. Approximately 49% of thimerosal is ethylmercury. Respondent Exhibit ["Res. Ex."] A at 2. Thimerosal is no longer used in most U.S. vaccines. Immunization Safety Review, VACCINES AND AUTISM, IOM, National Academies Press (2004) at 5-6 ["IOM 2004 Report"].

[17] Two additional cases, *Westfall v. Sec'y, HHS,* No. 99-439V, and *Schueman v. Sec'y, HHS*, No. 04-693V, involving the same injury filed, by other petitioners' counsel, were reassigned to me at a later time, and, at the request of petitioners' counsel in each of those cases, were added to this omnibus proceeding. I subsequently dismissed one of the 16 cases filed by Mr. Hennessey's counsel for reasons unrelated to the issue of causation. Two additional T1D cases, *Panzirer v. Sec'y, HHS*, No. 08-800V, filed on November 10, 2008, and *Jones v. Sec'y, HHS*, No. 09-197V, filed on April 1, 2009, were subsequently transferred to me. At the request of petitioner in *Panzirer*, it was added to this omnibus proceeding. A similar request in *Jones* has not yet been made.

than the specific vaccine administered. He opposed lifting the stays, indicating that he was not yet prepared to file an expert opinion supporting the theory of causation. After some discussion,[18] I ordered respondent to file a Vaccine Rule 4(c) report in each case and ordered the petitioners to file status reports providing specific information regarding ongoing studies that might link thimerosal-containing vaccines ["TCVs"] and T1D. I indicated that, based on the level of detail in the status reports and the identified timeline for release of studies, I would determine what action to take in each individual case. I reiterated that I did not intend to issue any further indefinite stays. Order, dated March 31, 2006.

On May 8, 2006, respondent filed a Vaccine Rule 4(c) report in the instant case, recommending that compensation be denied, noting gaps in the medical records filed, and contending that petitioner had failed to establish that any vaccine he had received contained thimerosal. Petitioner filed updated medical records on May 17, June 21, and October 10, 2006.[19] After receiving information concerning lot numbers and manufacturers of the vaccines petitioner received prior to his diagnosis, respondent filed a status report conceding that some of the vaccines received by petitioner contained thimerosal.[20] Respondent's Status Report ["Res. Status Rpt."], dated June 22, 2006. For three other vaccinations, petitioner was unable to produce information concerning the lot numbers and manufacturers, as petitioner's physician had not recorded that information. Pet. Ex. 13, p. 1.

On July 21, 2006, petitioner filed a lengthy response to the court's order of March 31, 2006, essentially urging the court to grant further delay in this case based on the Vaccine Act's "unusually strict statute of limitations"[21] (Petitioner's Response to Order of

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[18] Much of the discussion concerned lifting the stays in the T1D cases and requiring petitioners to produce evidence of vaccine causation. Petitioners' counsel urged me to provide additional time for the science to develop, an argument reiterated in subsequent filings. The difficulty with this argument is that if vaccines do not cause the conditions alleged, scientific evidence that they do will never be developed, and thus cases will remain open in perpetuity.

[19] Petitioner filed additional medical records on March 31, 2009. I have reviewed them and determined that they contain no additional information relevant to the significant aggravation claim. Thus, they are not included in the medical history summarized below.

[20] These included all three of the hepatitis B vaccinations petitioner received (two before his diagnosis and one after it) and the diphtheria, pertussis, and tetanus ["DPT"] vaccinations petitioner received on November 29, 1988, and June 19, 1992. Res. Status Rpt., dated June 22, 2006.

[21] Petitioner noted that "most states toll the statutes of limitations in favor of injured minors," meaning that most state statutes of limitations do not begin to run until the minor reaches the age of majority. Pet. Resp. at 2. In contrast, the Vaccine Act's three year statute of limitations begins to run on "the date of the occurrence of the first symptom or manifestation of onset or the significant aggravation of such injury." Section 300aa-16(a)(2). *Markovich v. Sec'y, HHS,* 477 F.3d 1353, 1357 (Fed. Cir. 2007). The statute also included a "look back" provision for new vaccines or Table injuries, which permitted claims for injuries occurring eight years prior to the effective date of revisions to the Vaccine Injury Table, if filed within two years of the statute's effective date. Section 300aa-16(b). When the hepatitis B vaccine

March 30, 2006 (sic) ["Pet. Resp."], at 3) and the Act's legislative history.[22] Petitioner also referred the court to the OAP and the theory, advanced by petitioners therein, that autism is a form of mercury poisoning, "specifically rel[ying] on all materials produced to date in the OAP as well as the expert reports [in the OAP] filed to date."[23] Pet. Resp. at 10. Petitioner argued that there was substantial evidence that vaccines and T1D were linked (Pet. Resp. at 13), but failed to cite to any specific article or study addressing the issue. Petitioner also listed a number of exhibits filed in an unrelated vaccine case, *Kolakowski v. Sec'y, HHS*, No. 99-625V, none of which concerned the role of vaccines

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was added to the Vaccine Injury Table, a similar eight year "look back" provision was included, based on the effective date of the tax on the vaccine. 62 FR 52724, Vol. 62, No. 196 (October 9, 1997).

Petitioner accurately argued that, in comparison with state codes, the statute is unusually strict, but failed to address why the strict statute of limitations is relevant to his argument that a petition should remain pending until "the science develops." Section 300aa-16(c) stays any state statute of limitations while a Vaccine Act petition is pending. If a petition is dismissed by a special master for failure to substantiate the claim, neither a minor nor an adult is in a worse position regarding the statute of limitations for any state cause of action.

Obviously, if the science has not yet developed sufficiently to support a causation claim under a state cause of action, the civil action will not be successful. However, the Vaccine Act contains no express or implied "right" to park a speculative claim (one in which no expert is presently prepared to opine in favor of vaccine causation) indefinitely in the Court of Federal Claims. If vaccines do not cause, or substantially contribute to, the development of a particular disease or condition, a petitioner will never develop scientific evidence supporting his claim. Under petitioner's argument, a petition might remain pending for decades, waiting in vain for the science to develop.

I also note that, past practice notwithstanding, the Vaccine Act requires that a petitioner file documents demonstrating vaccine causation with the petition. Section 300aa-11(c). This suggests that Congress expected petitioners to be able to substantiate their claims at the time they file their petitions.

[22] Rhetorically asking in his review of the purposes for the Vaccine Act why the court would "rush to judgment," petitioner apparently overlooked the statutory requirements for speedy resolution found in §§ 300aa-12(d)(2)(A) (vaccine rules shall "provide for less-adversarial, expeditious, and informal proceeding for the resolution of petitions" (emphasis added)); 300aa-12(d)(3)(A)(ii) (requiring a special master to decide cases "not later than 240 days...after the petition was filed); and 300aa-12(d)(3)(C) (granting a special master the authority to extend the 240 day period up to 180 days). While this statutory mandate for speedy resolution has been honored more in the breach than in practice, it is absurd to contend that requiring petitioner to fulfill his statutory duty (*see* § 300aa-11(c)) to substantiate a claim then more than five years old is a "rush" to judgment. As I indicated at the recorded status conference on March 24, 2006, and in my order of March 31, 2006, I was not precluding a grant of additional delay. Further delay, however, would have to be predicated on some evidence indicating that the connection between TCVs and T1D was, at a minimum, the subject of ongoing research.

[23] At the time this response was filed, no expert reports had been filed in the OAP. Some medical and scientific literature was filed in the OAP master file. *See, e.g.*, filings on December 8 and 13, 2006, and January 10, 2007, at the OAP Omnibus Docket website: www.uscfc.uscourts.gov/node/2718.

in the development of T1D.[24] Pet. Resp. at 14-23. Petitioner also referred the court to ongoing studies summarized on the American Diabetes Association website. Pet. Resp. at 24-26. None of these studies were examining the role of vaccinations or TCVs in development of T1D.[25]

In response, respondent argued, *inter alia*, that petitioner had failed to demonstrate any basis for keeping the T1D claims pending. Res. to Filing at 10. That argument became moot when, in response to my order of August 25, 2006, petitioner filed a status report on November 30, 2006, indicating that Dr. Yehuda Shoenfeld had reviewed several of the T1D cases and "rendered signed, preliminary opinions in each reviewed case linking the hepatitis B vaccine" to the petitioner's T1D.

In a status conference on January 19, 2007, counsel for both parties in 15 of the T1D cases agreed that petitioner's counsel would select a "test case" from among those 15 cases to be considered at an omnibus hearing. At this hearing, evidence would be developed on the issue of vaccine causation of T1D in general, in addition to the specific case selected. The general causation evidence could then be applied to the remaining cases. Mr. Hennessey's case was selected by his counsel as the test case. Thereafter, I set deadlines for the filing of expert reports. Order, dated February 1, 2007.

A hearing date in October, 2007, was set, but based on conflicts with hearings on the first theory of causation in the OAP, this case was reset for January 22-23, 2008. Doctor Shoenfeld testified for petitioner; Drs. Noel Maclaren, J. Lindsay Whitton, and Marian Rewers testified on behalf of respondent.[26] Respondent also filed the expert

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[24] Petitioner never filed these articles into the record of this case. I reviewed the articles filed in the *Kolakowski* case in preparation for the status conference, but have not considered them as evidence of causation (or lack thereof) in this case. None of these articles, nor any of the hundreds of articles that were filed into the OAP master file or in any of the autism test cases, were specifically cited by petitioner or his expert in support of his position on causation in this case. Thus, in considering the "record as a whole" in this case, I have not relied upon scientific or medical studies, textbooks, or other materials not filed as exhibits in this case, unless otherwise noted.

[25] At Tab A of his Response to Petitioner's Filing of July 21, 2006 ["Res. to Filing"], respondent included a copy of the research description for each of these studies. As set forth in my Order, dated August 25, 2006, I visited the American Diabetes Association website and employed their search engine to determine if that website contained any information on studies of vaccine causation of T1D, with negative results. It appeared that several studies were examining whether a vaccine against T1D might be efficacious, but none were specifically examining whether vaccines cause T1D. Hearing evidence indicated that data on vaccines received are included among a large number of environmental factors in a prospective cohort study, but vaccines are not that study's primary focus as potential causative factors. Transcript ["Tr."] at 330-31. The testimony of Dr. Rewers (the co-director of one such study's steering committee) was that vaccines in use for some period of time no longer warranted serious consideration as causal factors, but the vaccines more recently approved for administration to children were being evaluated, along with other potential environmental risk factors. Tr. at 300-01.

[26] The qualifications of these experts are detailed, *infra*.

report of Dr. Barry Bercu, but he did not testify at the hearing.

The hearing testimony focused both on the basis for Mr. Hennessey's claim and on the issue of vaccine causation of T1D in general. I begin with Mr. Hennessey's medical history, as set forth in his medical records and as explained by the expert witnesses.

II. Medical History.

Mr. Hennessey was born on May 25, 1987. Petitioner's Exhibit ["Pet. Ex."] 1, p. 1. Although prenatal records were not filed in this case, there is nothing in his neonatal records to indicate that there were any gestational difficulties. He experienced the usual childhood illnesses, including upper respiratory infections, bouts of otitis media, warts, bronchitis, sprains, and fevers. *See generally*, Pet. Exs. 2, 3, and 12. He had tympanostomy tubes inserted when he was just under one year old. Pet. Ex. 12, p. 24. Mr. Hennessey received the usual childhood vaccinations, including DPT, oral polio ["OPV"], measles, mumps, and rubella ["MMR"], and hemophilus influenzae b ["Hib"]. Pet. Ex. 12, p. 1. His last vaccinations, prior to the 1998 receipt of the two hepatitis B vaccinations alleged to be causal, occurred on June 19, 1992, when he received DPT and OPV.

Mr. Hennessey was a generally healthy and active child. Pet. Ex. 8, ¶ 1. In the months prior to his first hepatitis B vaccination, there were several physician visits. He had an eye examination in June, 1998. Pet. Ex. 7, p. 1. In July, 1998, he developed an upper respiratory infection and otitis media.[27] His physician apparently considered the illness viral, rather than bacterial, in origin, because he prescribed symptomatic treatment, rather than antibiotics. Pet. Ex. 2, p. 1. One of the expert witnesses noted that Mr. Hennessey's rate of growth had declined in the two years preceding his first hepatitis B vaccination. Tr. at 164-65.

On September 15, 1998, Mr. Hennessy, then 11 years old, received his first hepatitis B vaccination. Pet. Ex. 1, p. 1. According to his mother's affidavit, he experienced no observable reactions. Pet. Ex. 8, ¶ 2. He received his second hepatitis B vaccination on November 17, 1998. Pet. Ex. 1, p. 1. Although there was no reaction to the vaccine noted in his medical records, his mother believed that his stamina decreased during the autumn months, and that this diminution of energy became more pronounced after the second vaccination. According to his mother's affidavit, by

[27] Respondent's experts relied upon circumstantial evidence to indicate that Mr. Hennessey was experiencing an enterovirus infection at this visit. Respondent's Post-Hearing Submission at 20-21. The nature of this infection is significant to the issue of alternate cause, but the issue of alternate cause itself comes into play only if petitioner established a *prima facie* case for vaccine causation. Because I conclude that petitioner has failed to establish a *prima facie* case for causation under *Althen's* three factor test, the burden never shifted to respondent to establish an alternate cause. Nevertheless, I discuss respondent's alternate cause case in Section IV(E), below.

November 19, 1998, he had developed classic symptoms of diabetes, including weight loss and excessive thirst and urination. Pet. Ex. 8, ¶¶ 3-4. She described his excessive thirst at their Thanksgiving Day dinner. *Id.*, ¶ 4. I judicially note that, in 1998, Thanksgiving Day was on November 26.

He saw his family physician on November 30, 1998. At that time, his mother reported a several week history of increased thirst and urination and a four pound weight loss since the beginning of the school year.[28] She reported no family history of diabetes. After laboratory tests revealed extremely high blood and urinary glucose levels and ketones in his urine,[29] his doctor diagnosed him with new onset T1D and referred him to St. Paul Children's Hospital. Pet. Ex. 4, p. 3.

Mr. Hennessey was admitted to Children's Hospital that same day. A history taken upon admission noted increased thirst and urination beginning approximately a week and a half earlier, placing onset of symptoms shortly after Mr. Hennessey's second hepatitis B vaccination. Pet. Ex. 10, pp. 4, 7.

On the day he was admitted, a laboratory report summary sheet reflected a hemoglobin A_{Ic} ["HB A_{Ic}"] level of 12.1%.[30] Pet. Ex. 5, p. 1. After treatment to determine the level of insulin required to control his blood glucose levels, Mr. Hennessey was discharged on December 3, 1998, with a diagnosis of T1D under good control. Pet. Ex. 10, pp. 7-8.

Mr. Hennessey was next seen by his pediatric endocrinologist on December 16, 1998, a little over two weeks after his diagnosis. His blood glucose[31] levels remained under excellent control during this period, as indicated by the decline in his HB A_{Ic} level to 11.7%. Mr. Hennessey also reported that his vision had improved. Pet. Ex. 5, p. 12.

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[28] As the medical records demonstrated, the weight loss was actually much more severe. Mr. Hennessey weighed about 88 pounds at the beginning of the school year, according to the patient history, but weighed only 78 pounds upon admission to Children's Hospital on November 30, 1998. Pet. Exs. 4, p. 3 and 5, p. 12.

[29] Mr. Hennessey's blood glucose was 571 milligrams per decaliter ["mg/dL"], flagged as a "critical" level (Pet. Ex. 4, p. 3) and his urinary glucose was literally "off the chart," with a reading of more than 1000 mg/dL. *Id*., p. 7.

[30] Hemoglobin A_{Ic} is a minor red blood cell constituent that comprises 5% of the total hemoglobin in the blood of normal individuals. The percentage may be as high as 15% in patients with diabetes. Older red cells contain the most HB A_{Ic}; the actual percentage is a function of red cell half life and the rate of HB A_{Ic} synthesis, which in turn is determined by the blood glucose concentration. Respondent's Exhibit ["Res. Ex."] AA at 29-30. *See also* Tr. at 166-70A and discussion, *infra*.

[31] The terms "blood glucose" and "blood sugar" were used interchangeably by the experts. I use the term blood glucose throughout this opinion to avoid any confusion caused by the use of different terms.

Mr. Hennessey received his third hepatitis B vaccination on January 19, 1999.[32] Pet. Ex. 1, p. 1. Followup care over the next year indicated that Mr. Hennessey's diabetes remained under good to reasonable control, with comments that he remained in his diabetic "honeymoon" period.[33] *See, e.g.*, Pet. Ex. 5, pp. 9, 15. His HB A_{1c} levels declined from the high of 12.1% upon his initial diagnosis, to a low of 6.9% in March, 1999, rising to 8.4% in June, 1999, and remaining relatively steady at 7-8% through December, 1999. Pet. Ex. 5, p.1.

During his December, 1999, followup visit, Mr. Hennessey was screened for celiac disease.[34] The screening test was positive and his pediatric endocrinologist, Dr. Jennifer Kyllo, recommended that he see a gastroenterologist. Pet. Ex. 5, p. 19. An endoscopy and small bowel biopsy were performed on March 6, 2000, with results consistent with celiac sprue, including severe villous atrophy with crypt hyperplasia. Pet. Ex. 6, pp. 8-9. He was placed on a gluten-free diet. *Id.*, p. 4.

Over the next year, Mr. Hennessey's blood glucose remained under good control. *See, e.g.*, Pet. Ex. 15, pp. 81, 85. However, beginning in 2001, he developed difficulty in controlling his blood glucose, experiencing frequent hypoglycemia.[35] *Id.*, pp. 76-77, 79. By mid-2002, he was experiencing large fluctuations in blood glucose levels. *Id.*, p. 67. This problem persisted into 2003. *Id.*, p. 46. In July, 2004, he had an episode of severe hypoglycemia, requiring emergency medical assistance. Pet. Ex. 22, pp. 2-4. He was seen in an emergency room for hypoglycemia in August, 2005, and

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[32] In Ms. Hennessey's affidavit, Pet. Ex. 8, ¶ 5, she described questioning whether her son should receive this third hepatitis B vaccine, and being told by Mr. Hennessey's medical team that he should receive the vaccination because "the damage had already been done." In view of the uncontested medical evidence that the insulin-producing β cells do not regenerate, and that Mr. Hennessey was already incapable of producing sufficient insulin to sustain him at the time of the third vaccination, I do not interpret this statement as evincing any opinion by the treating medical team regarding vaccine causation of his condition. In view of Dr. Shoenfeld's opinion that a vaccine after clinical onset of T1D could adversely affect the diabetic "honeymoon" period (discussed, *infra*), this reported statement by one of Mr. Hennessey's treating physicians that a third vaccine would not affect his T1D could be interpreted as an opinion adverse to Dr. Shoenfeld's. However, I do not attach any causal significance to this report.

[33] At initial diagnosis, most T1D patients still retain some ability to produce insulin, although they produce insufficient amounts to fully control blood glucose levels. The period during which a Type 1 diabetic still produces some insulin is referred to as the "honeymoon" period, a time during which blood glucose control is more easily achieved. Later, when little or no insulin is produced naturally, glucose control becomes more difficult. Tr. at 239-40.

[34] Celiac disease, sometimes called celiac sprue or gluten sensitive enteropathy, is characterized by an inability to digest gluten (found in wheat, barley, and rye products). DORLAND'S ILLUSTRATED MEDICAL DICTIONARY ["DORLAND'S"] at 530 (30th ed. 2003). *See also* Pet. Ex. 6, p. 2. Approximately 1-3% of T1D patients also have celiac disease, a much higher percentage than found in the non-diabetic population. Those at high genetic risk for T1D are at a similar genetic risk for celiac disease.

[35] "Hypoglycemia" is low blood glucose; "hyperglycemia" is high blood glucose. Either condition can lead to complications. DORLAND'S at 894, 881.

again in July, 2006. Pet. Ex. 17, p. 7; Pet. Ex. 23, p. 3. The July 2006 incident was more serious, as Mr. Hennessey experienced two seizures due to low blood glucose. Pet. Ex. 23, pp. 3-4.

Mr. Hennessey played high school and college football, experiencing several sports related injuries. *See*, *e.g.*, Pet. Exs. 17, p.12; 20, pp. 5-7; 22, pp. 10, 12-17. Other than treatment for his diabetes and sports injuries, his post-diagnosis medical history was remarkable only for one episode of unexplained muscle weakness, lasting for about a month in May, 2000, which was possibly related to his diabetes. The remainder of his medical records, including some recently filed, are not relevant to the issue of causation.

III. Causation Evidence.

A. In General.

The evidentiary record in this case includes the reports and testimony of experts with extraordinary credentials in their fields. In addition to the testimony of four expert witnesses and the written report of a fifth expert, over 200 medical and scientific journal articles were filed into the record. Many of these articles were discussed during the causation hearing and in the expert reports. The analysis of the evidence pertaining to causation begins with the experts themselves, moves to a discussion of the two conditions from which Mr. Hennessey suffers, and the evidence concerning causation in Mr. Hennessey's particular case. This evidentiary discussion, of necessity, addresses the general causation questions raised in other T1D cases. It does not, however, resolve all of the issues likely to be raised in the additional T1D cases.

B. The Expert Witnesses.

1. Doctor Yehuda Shoenfeld.

Petitioner's expert witness was Dr. Yehuda Shoenfeld, a clinical immunologist who specializes in autoimmune diseases. He completed a residency in internal medicine and did post-doctoral research on autoimmune diseases at Tufts University, focusing on experimental models of autoimmune diseases. He is currently the head of the Department of Medicine and the Center for Autoimmune Diseases at Sheba Medical Center in Israel. Tr. at 8-9.

Doctor Shoenfeld has an active clinical practice, treating patients with conditions as diverse as myocardial infarction and pneumonia. He also sees patients at a

multidisciplinary center for autoimmune diseases, including Type 1 diabetes.[36] The center has a large research laboratory devoted to research on autoimmune diseases, research in which Dr. Shoenfeld is actively involved. The laboratory publishes 30-50 papers per year in peer reviewed journals. Tr. at 9-12.

Doctor Shoenfeld has authored and edited textbooks, chapters in other textbooks, and is the editor of two journals dealing with autoimmune diseases. He lectures extensively, is a full professor, and shares many patents related to autoimmunity with other researchers in his laboratory. He received the Eular Prize for his work in determining the infectious origin of antiphospholipid antibody syndrome. Tr. at 12-14. His many journal articles are included in his curriculum vitae ["CV"] at Pet. Ex. 24, pp. 31-92, and his own journal articles form a substantial number of the attachments to his expert report, filed as Pet. Ex. 45.[37]

Although Dr. Shoenfeld's research interests and clinical practice focus on autoimmune diseases in general, rather than on T1D in particular, he explained that he considers all autoimmune diseases to be the same disease, whether T1D or systemic lupus erythematosus ["SLE"].[38] His theory that all autoimmune diseases are the same condition is illustrated by the application of therapies for one autoimmune disease to other such diseases. Tr. at 10. For example, Rituximab, a drug which was originally given to patients with lymphoma, has since been used in treating SLE and more than 50 other autoimmune diseases. Tr. at 21. There was no evidence, however, that T1D is among those diseases.

I found Dr. Shoenfeld to be a very highly qualified immunologist, with significant expertise on autoimmune conditions in general. However, he was less experienced in diagnosing and treating T1D than several of respondent's experts, has conducted no research directly related to T1D causation, and has not published anything, other than literature surveys, directly related to T1D. Indeed, many of his listed publications are

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[36] The record is unclear concerning how many T1D patients Dr. Shoenfeld actually treats or whether he is involved in diagnosing T1D on any regular basis. It does not appear that T1D patients form a substantial part of his practice. His research focus appears to be on autoimmune diseases in general, rather than on T1D in particular. He does not treat children with diabetes, although he treats patients with diabetes when they are over 16. Tr. at 80.

[37] Petitioner inadvertently labeled two exhibits "Exhibit 45," Dr. Shoenfeld's report and a scientific journal article by Von Herrath, *et al.* To minimize confusion, I will use "Pet. Ex. 45" throughout this opinion to refer solely to Dr. Shoenfeld's report.

[38] Commonly known as "lupus," systemic lupus erythematosus is a chronic inflammatory disease. It is characterized by severe vasculitis, renal problems, and skin and nervous system lesions. Its cause is unknown, but both immune system disorders and viral infections have been suggested as possible causes, and lupus-like reactions to certain drugs have been noted. Diagnosis is based on objective physical examination and laboratory tests for antinuclear antibody in the cerebrospinal fluid and a positive lupus erythematosus cell reaction, as well as on subjective findings. MOSBY'S MEDICAL DICTIONARY at 1813 (7th ed. 2006).

literature surveys, rather than original research. Of the approximately 20-25 patients Dr. Shoenfeld sees on a daily basis, nearly all are adults. Of the autoimmune disease patients he sees, approximately a quarter are children. He does not actively manage patients with diabetes, although he does see patients with the disease. His role in T1D is part of his role in the Internal Medicine Department at Sheba Medical Center. There is no Department of Endocrinology in his hospital.[39] Tr. at 79-80.

2. Doctor Noel Maclaren.

Doctor Maclaren's curriculum vitae was filed as Res. Ex. SS. He has thirty years of medical experience, having trained in pediatric endocrinology in London and at Johns Hopkins. Early in his career, he started a research group at the University of Florida into the epidemiology of T1D. His research examined the long latency period for development of T1D and the predictive nature of autoantibodies. Currently, he is a full professor of medicine at Cornell University.

Doctor Maclaren's current focus is his clinical practice, which is limited to adults and children with endocrine diseases, primarily diabetes. He sees approximately 20 patients a day, about 25% of whom are children with T1D. He currently treats about 15 patients who, like Mr. Hennessey, have both T1D and celiac disease.

Although less focused now on research than in the past, Dr. Maclaren continues to teach and write on T1D. He has received a number of research grants from the National Institutes of Health ["NIH"] for his work investigating T1D. Doctor Maclaren is the recipient of the Canadian Diabetes Association's award as International Diabetes Investigator of the Year and the Juvenile Diabetes Foundation International's Diabetes Researcher of the Year for 1995. Tr. at 135-39; Res. Ex. SS.

Dr. Maclaren was one of the reviewers on the Institute of Medicine's 2002 report on multiple immunizations and immune dysfunction (which included T1D)[40] and he was a participant in two additional meetings of researchers examining the postulated connection between T1D and vaccines. As a reviewer, Dr. Maclaren's role was to examine all of the published literature worldwide on vaccines and T1D. Tr. at 139-40.

I found Dr. Maclaren to be a highly qualified expert witness, with significant research credentials into T1D's causes and strong clinical experience in the diagnosis and treatment of T1D.

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[39] In the U.S., T1D is commonly treated by endocrinologists, not immunologists. *See* Pet. Ex. 4, p. 3 (noting Mr. Hennessey's referral to Dr. Kyllo) and Pet. Ex. 5, p. 19 (letter from Dr. Kyllo indicating her speciality in pediatric endocrinology and diabetes)

[40] K. Stratton, *et al.*, eds., IMMUNIZATION SAFETY REVIEW, *Multiple Immunizations and Immune Dysfunction*, INSTITUTE OF MEDICINE, National Academy Press, Washington, DC (2002) ["2002 IOM Report"].

3. Doctor Marion Rewers.

Doctor Rewers graduated from medical school in Poland, where his volunteer service at a camp for diabetic children sparked an interest in the disease. He completed a residency in pediatrics and a fellowship in pediatric endocrinology. During his fellowship with the American Diabetes Association in Pittsburgh, he also completed a masters degree in Public Health. He moved to the U.S. to accept a faculty appointment at the University of Colorado in 1990. Tr. at 244-46, Res. Ex. BBB.

He is currently a professor at the University of Colorado Health Sciences Center, where he has served since 2000 as the clinical director of the Barbara Davis Center for Childhood Diabetes. The center is the largest research and outpatient institution for T1D in the U.S., and is largely funded by NIH grants and contracts, income from clinical services, and charitable donations. The clinic sees about 5,000 patients with T1D, including approximately 3,600 children. Prior to becoming the director of the diabetes center, he was on the faculty at the University of Colorado's medical school, rising to full professor in the Department of Preventive Medicine and Biometrics. Tr. at 242-45.

Doctor Rewers supervises a staff of 50 clinical providers, including 18 physicians and a staff of 80-100 research assistants involved with clinical research. As a practicing pediatric endocrinologist, he spends approximately 20% of his time in clinical practice. The remainder is devoted to research and administration of the center. Tr. at 243-44.

As a part of his Ph.D. research on adolescents with insulin pumps, he published his first paper, measuring physiologic responses to infusion rates, exercise, and diet, in 1984. Tr. at 245. He continues to have teaching responsibilities on a one-on-one basis, rather than in a classroom setting. He has previously taught cardiovascular disease epidemiology, chronic disease epidemiology, and advanced epidemiology. He has received awards from the American Diabetes Association as a junior investigator and received the Kelly West Award, which is the highest honor bestowed worldwide in the field of diabetes epidemiology. Tr. at 244, 247-48.

His public health focus began in descriptive epidemiology, looking at the incidence by country of T1D by birth cohort, and progressed to analytical epidemiology, which looks for disease causes by examining risk factors in case-control or cohort studies. His subspecialty is in cohort studies, which involve enrolling a large number of children at birth who are at risk for disease and following them for many years to study what environmental exposures change their health status. In the case of T1D, this includes studying the development of autoantibodies and the subsequent development of T1D or celiac disease. Tr. at 246-47.

Doctor Rewers was offered as an expert in epidemiology and pediatric endocrinology without objection. Tr. at 250. I found Dr. Rewers to be a highly qualified expert witness, who offered careful, focused, and highly credible testimony.

4. Doctor J. Lindsey Whitton.

Doctor Whitton entered medical school at the University of Glasgow, Scotland, when he was 16, but took a leave of absence for several years to obtain a bachelors degree in molecular biology, with a specialization in molecular virology. He then returned to medical school, graduating in 1979. After completing his internship, he obtained a Ph.D. in molecular virology, and was then offered a postdoctoral fellowship with Dr. Michael Oldstone, a world leader in the study of how viruses cause disease, at the Scripps Research Institute. Tr. at 339-40, Res. Ex. Y.

He is currently employed as a professor at the Scripps Research Institute in La Jolla, CA, where his primary focus is on research. The Scripps Institute is a dedicated research facility with a small teaching program. His responsibilities include raising funds to support his virology and immunology research, including vaccine research. He recruits and trains postdoctoral fellows and technicians. Within his department, approximately 50% of the faculty study viral infections, focusing on infections of the central nervous system. The remaining faculty study behavior, classical neural pharmacology, and neural electrophysiology. Tr. at 336-39.

For the last 20 years, various NIH grants have supported Dr. Whitton's study of T-cell responses to viral infections, coxsackie virus pathogenesis, viruses and autoimmunity, and vaccine research. He served as the chair of an NIH study section on multicomponent vaccines, reviewing and selecting grant applications for funding. He served for many years on the NIH virology study section. He has been a member for more than a decade of the editorial boards of the two leading virology journals in the world. He is an editor of *Virology*, and was asked to serve as an editor of *The Journal of Virology*, but declined the honor. Tr. at 343-45.

Doctor Whitton was offered as an expert in the fields of immunology and virology. Tr. at 345. His expert report was filed as Res. Ex. X. He was an exceptionally good expert witness, one who made difficult immunologic concepts readily understandable. His thoughtful (and helpful) responses to questions both on cross-examination and from the court could serve as a model for what expert testimony should be, and unfortunately, so rarely is.

5. Doctor Barry Bercu.

Although Dr. Bercu did not offer hearing testimony, his expert report was filed as Res. Ex. A and his CV was filed as Res. Ex. B. Doctor Bercu is a professor of Pediatrics and Molecular Pharmacology and Physiology at the University of South Florida's College of Medicine. He earned his M.D. at the University of Maryland in 1969 and is board certified in pediatrics and pediatric endocrinology. After completing his residency in pediatrics at Massachusetts General Hospital, he spent three years, from 1974-1977, as a clinical research fellow in pediatric endocrinology and metabolism at Harvard Medical School and in endocrinology in the Department of Internal Medicine at

Tufts University Medical School. Doctor Bercu currently serves on the editorial boards of four medical journals and has published almost 150 medical journal articles.

C. The Disease of Type 1 Diabetes.

In order to place the evidence on causation in context, some background information concerning the natural history of T1D is necessary. The following factual findings concerning T1D were largely uncontested.

1. Diabetes in General.

Diabetes is not a disease in the classic sense. It is a condition characterized by elevated blood glucose as the result of some underlying disease process. About eighty different diseases can cause elevated blood glucose. Type 1 diabetes is caused by a decrease in the secretion of insulin, leading to an elevation of blood glucose. Decreased insulin secretion may be caused by a dominantly inherited genetic disorder, an autoimmune process, or a direct viral attack that causes destruction of the insulin-producing β islet cells of the pancreas. The β islet cell destruction leads to progressive insulin insufficiency, causing a rise in blood glucose levels. Tr. at 142-43.

Type 1 diabetes is the third most prevalent severe chronic childhood disease. It affects approximately 0.3% of children and young adults by age 20. Res. Ex. AAA at 2. Although it is commonly considered a disease developed in childhood, T1D has been diagnosed in infants as well as in octogenarians. In some cases, the cause (if not the exact biologic mechanism) of the β islet cell destruction can be determined, such as in congenital rubella (Tr. at 31A, 43, 374A), but in most cases, no specific cause is ever identified. Several aspects of the natural history of the disease have provided clues and fueled research efforts to identify the cause or causes, prevent future cases, and develop better treatment options.

2. Pathogenesis, Testing, and Diagnosis.

a. β Islet Cell Destruction.

Pancreatic β cells are balls of specialized cells found in the pancreatic islets, scattered throughout the pancreas. The pancreas itself secretes digestive fluid into the digestive system; the islets secrete a hormone called insulin directly into the bloodstream in response to a rise in blood glucose levels, such as those occurring after a meal. Tr. at 143.

Insulin transports glucose from the blood into muscle tissue, where the glucose is burned as fuel. If insulin production is insufficient, the blood glucose cannot be transported out of the bloodstream and into tissue. Blood glucose levels continue to increase, while muscle tissue is starved, and the body begins to burn fat as fuel. As body fat is broken down, fatty acids are metabolized into ketone bodies, which pass into

the urine. There, they drain salted water (saline) from the body, leading to dehydration. In effect, a person with insufficient insulin production starves, in spite of adequate food consumption, because the glucose that is produced by digestion cannot be transported to the muscles for use as fuel. Tr. at 144-45.

In T1D, insulin production is gradually reduced by the destruction of the β islet cells that produce it. Tr. at 56. In most cases of T1D, the islet cells are destroyed by "friendly fire," in that they are attacked by cytotoxic T cells (CD8+ cells)[41] which are a part of the body's adaptive immune system. Thus, most cases of T1D are the result of a cell-mediated autoimmune disease process. Tr. at 16, 81, 447A-49B.

In a small number of cases of T1D, some researchers believe that the β islet cells are destroyed in a direct viral attack, rather than by an autoimmune response. Some individuals with congenital rubella syndrome develop T1D. Because the rubella virus has been detected in the islet cells, a direct viral attack is suspected to be the cause of the islet cell destruction, although an immune attack focused on the virus-infected cells is possible. Tr. at 31A, 43, 374A, 448A-49B. Only congenital rubella appears to be associated with T1D, which suggests either an autoimmune etiology or a narrow window of susceptibility. Congenital rubella is also associated with other autoimmune disorders. G. Eisenbarth, Chapter 23, *Type 1 Diabetes Mellitus*, JOSLIN'S DIABETES MELLITUS ["Eisenbarth"], filed as Res. Ex. Q, at 407-08.

There are two subtypes of T1D, Type 1A (autoimmune) and Type 1B (idiopathic). The natural history of both types is that of a progressive disease, with eventual insulin dependence, but Type 1B appears without any evidence of an autoimmune disorder. *See* P. Bennett and W. Knowler, Chapter 19, *Definition, Diagnosis, and Classification of Diabetes Mellitus and Glucose Homeostasis*, JOSLIN'S DIABETES MELLITUS, ["Bennett and Knowler"], filed as Res. Ex. P, at 333. Mr. Hennessey likely has Type 1A diabetes, based on the co-occurrence of celiac disease, another autoimmune disorder. The predominant form of T1D is the autoimmune type. *See* Eisenbarth, Res. Ex. Q, at 399.[42]

In most cases, the β islet cells are destroyed gradually, and there is often a lengthy period during which the remaining β islet cells continue to produce sufficient insulin to keep blood glucose levels within normal limits. However, the loss of some cells requires the remaining cells to work harder to produce sufficient insulin, further stressing those remaining cells. When 50-75% of the β islet cells are destroyed, clinical symptoms of T1D, including fatigue, thirst, and frequent urination appear. Tr. at

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[41] CD8 T-cells are cytotoxic or killer T-cells. CD4+ T-cells are the helper T-cells, or TH-cells. Tr. at 340-41.

[42] I note that the author of this chapter acknowledged the contributions of Dr. Rewers, and thanked him for his suggestions concerning the environmental factors involved in the pathogenesis of T1D. Eisenbarth, Res. Ex. Q, at 418.

145,162-64, 239.

Histologic examination of the pancreas at the time of clinically apparent symptoms shows most islets deficient in β cells, with a condition known as insulitis in those islets with β cells remaining. Insulitis is a chronic inflammatory infiltrate consisting primarily of CD8 T cells, and other immune system cells, including variable numbers of CD4 T cells, B lymphocytes, macrophages, and natural killer cells. The distribution of islets with insulitis is often variable, with affected islets adjacent to islets with no visible signs of insulitis. Res. Ex. TT[43] at 1429; DORLAND'S at 939.

b. Symptoms and Diagnosis.

Type 1 diabetes begins with a long latency, or prodromal, period of months to years, during which blood glucose levels slowly rise without obvious symptoms. As the blood glucose levels consistently exceed 200, symptoms begin to be observed. Tr. at 188-90. A blood glucose level of 180-200 is necessary before there is spillover of sugar into the urine, leading to polyuria (increased urination). However, the increase in the volume of urine would be barely noticeable by a person with T1D at the 200 milligram per decaliter threshold. As the fat breakdown occurs, urinary ketones drain salt from the body, leading to unusual thirst (polydypsia). Tr. at 145-47A, 235-36. Glucose levels in other bodily tissues, particularly the eyes, also rise as blood glucose levels rise. Blurred vision indicates a period of three months or more of high glucose. Tr. at 257-58, 314.

Diabetes may be diagnosed from a combination of clinical symptoms (polyuria, polydypsia, fatigue or reduced energy, weight loss, vision change, and others), plus a blood glucose level over 200 milligrams per decaliter of blood. It may also be diagnosed in the absence of clinical symptoms, based on two tests showing high blood glucose levels. Tr. at 145-47A, 233. Those tests include a fasting blood glucose over 125 and a postprandial blood glucose level measuring over 200 two hours after a glucose challenge.[44] High blood glucose in humans is often initially detected through urine glucose testing. At blood glucose levels in excess of 180, some glucose is

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[43] M. Atkinson and N. Maclaren, *The Pathogenesis of Insulin-Dependent Diabetes Mellitus,* NEJM 331: 1428-36 (1994). The second author is the same Dr. Maclaren who testified as an expert witness in this case.

[44] In healthy individuals, fasting blood glucoses are usually less than 105. Postprandial blood glucose levels are usually no more than 140. Tr. at 143. *See also* K. Pagona and T. Pagona, MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS ["MOSBY'S LABS"] at 267, 271 (3d. ed. 2006). Doctor Shoenfeld testified that the normal fasting blood glucose level would be 100-120. He also testified that a blood glucose level of 250 would not be an indication of diabetes, simply a suspicion, although he agreed that a level of 250 is outside the normal range. Tr. at 88. To the extent that Dr. Shoenfeld's testimony on the level of blood glucose sufficient to be diagnostic of diabetes differed from that of Drs. Maclaren or Rewers, I credited their testimony over that of Dr. Shoenfeld, based on their greater research and clinical experience with diabetes. Tr. at 145-46, 166, 171A.

removed from the blood through the kidneys, resulting in urinary glucose, detectable by a simple screening test. As the normal value for urinary glucose is zero, diabetes is strongly suspected if there is any level of glucose in the urine. Tr. at 188-90, 236, 277.

c. Hemoglobin A_{lc}.

When the pancreatic β islet cells are functioning normally, a small percentage of the blood glucose binds to red blood cells as they are formed, producing a type of hemoglobin known as HB A_{lc}.[45] A normal HB A_{lc} level is 5%. As insulin production declines as the result of β islet cell destruction, blood glucose levels rise, and, thus, more glucose is available to bind to hemoglobin, resulting in an increased percentage of HB A_{lc} in the blood. An HB A_{lc} percentage in excess of 6.5% is also diagnostic of diabetes, even in the absence of clinical symptoms. As an HB A_{lc} test represents an average of blood glucose levels over the preceding three to four months, only one test is required for diagnosis, unlike direct measurements of current blood glucose levels (spot readings), which require elevated glucose levels on separate days for diagnosis, in the absence of clinical symptoms. Tr. at 166-70A, 203-04.

d. Complications of T1D.

Complications from T1D include vision, nerve, and kidney damage, which are probably initiated by glycosylation of body proteins. Glycosylation or glycation means that glucose is added to the proteins found in the membranes of small blood vessels, especially arteries. This causes the blood vessels to leak. The large arteries may also be affected. In the eye, the blood vessels bulge, causing retinopathy. High blood glucose levels may also cause cataracts. Diabetes is the leading cause of blindness in the U.S. Those with T1D are predisposed to strokes and heart attacks. Tr. at 148B-51.

The peripheral nerves of the feet are often affected, causing numbness. The foot may become injured without the individual being aware of the injury. The kidneys are also affected, often progressively, reducing kidney function. Diabetes is the leading cause of end stage renal disease. Tr. at 148-50.

[45] Once glucose binds to hemoglobin to create HB A_{lc}, it remains bound until the cell dies. Red blood cells have a life span of three to four months; thus the HB A_{lc} level can be used to calculate the average blood glucose level over this same period. According to all the experts and the filed medical literature, the HB A_{lc} reading is commonly used by health care providers and researchers as an accurate measurement of average blood glucose readings over the preceding three to four months. It represents a much more accurate assessment of the level of control of blood glucose levels than the spot recordings logged by diabetics. Tr. at 203-04, 347, 377, 435A-438A, 456B-459.

The end stage of untreated diabetes from the progressive loss of pancreatic islet cells begins with diabetic ketoacidosis.[46] Diabetic ketoacidosis is now uncommon because routine blood or urine glucose tests generally identify diabetes prior to the onset of symptoms. Tr. at 145-47A. Autopsies of patients who died of diabetic ketoacidosis showed lymphocytic infiltrates in the pancreatic islets and the loss of approximately 50-70% of the islet cells at the time of death. Tr. at 160-61.

At the time of his diagnosis, Mr. Hennessey was in a state of diabetic ketoacidosis. As Dr. Maclaren described his clinical presentation: "The character of the clinical onset (ketosis, dehydration) was indicative of an advanced loss of insulin secreting pancreatic β cells...". Res. Ex. RR at 4.

3. Identification of Those At Risk.

Two scientific advances have aided in the identification of those at risk of developing T1D and research into the causes of T1D. First, certain genes are strongly associated with the development of T1D. Thus, genetic testing may identify those at high risk. Second, the discovery that the presence of certain autoantibodies are predictive of the risk of developing T1D has helped with the early identification of those at risk. While many healthy individuals have transient "pre-diabetic" autoantibodies but do not develop T1D, the presence of two or more of these autoantibodies signals an almost inevitable progression to insulin dependence. Tr. at 151-60.

a. Autoimmunity and T1D.

All of the experts agreed that T1D is generally, although not exclusively, an autoimmune disease. Doctor Noel Rose, whom Dr. Shoenfeld characterized as the "father of autoimmunity" (Tr. at 13), described the four criteria by which a disease is classified as an autoimmune condition: a genetic background; the ability to transfer the disease from one individual to another by the transfer of cells or pathogenic autoantibodies; an environmental inducement or trigger; and a hormonal component. Type 1 diabetes fulfills all four criteria. The disease can be transferred by autoreactive cells from one animal to another, which is one of the cardinal signs by which an autoimmune disease is recognized. Tr. at 6-19.

In an autoimmune disease, the immune system malfunctions and cells designed to attack invading pathogens begin attacking the body's own tissue. Tr. at 18, 24-25. This is sometimes referred to as "breaking tolerance," referring to the immune system's normal tolerance for host tissue. Tr. at 35. Such attacks may be organ-specific, as in T1D, or may be more systemic, as in SLE. The type of genetic background necessary

[46] Diabetic ketoacidosis is characterized by polyuria, polydypsia, ketone bodies in the urine, and dehydration. It may cause brain edema, leading to seizures. The condition may be fatal, even if recognized and treated. Tr. at 147A.

to develop the disease differs from one disease to another. Those with a genetic susceptibility to a particular autoimmune disease do not invariably develop the disease. Tr. at 18-20. For example, individuals with HLA A1BADR3 are ten times more likely to develop an autoimmune disease than those without that HLA. However, many people with that particular HLA type do not develop an autoimmune disease, because they do not encounter a triggering mechanism or do not have other unknown factors needed to induce the disease. Tr. at 23-24.

b. The Genetics of Diabetes.

As in most diseases in which genetics plays a role, the study of identical twins has proven instructive. The concordance rate–the rate at which both twins develop the same disease–in T1D is approximately 33%.[47] Res. Ex. TT at 1428. If the disease were purely genetic, the concordance rate would approach 100%. First degree relatives (children or siblings) of those with T1D diabetes are only slightly more likely to develop the disease than those with no family history. Tr. at 57A-58A. Ninety percent of the patients newly diagnosed with T1D do not have a first degree relative with the disease. Res. Ex. TT at 1428.

The primary gene associated with a predisposition to develop T1D is located on the short arm of chromosome 6, in an area associated with the human leukocyte antigen ["HLA"] molecules. The HLA genotype of an individual affects the ability to respond and degree of response to a particular antigen. Variations in these genes may predispose someone to T1D, as well as being predictive of the development of T1D. Tr. at 151-52A; Res. Ex. TT at 1428. A second gene conferring susceptibility to T1D is located on chromosome 11, in front of the insulin gene. There are many other genes that may have minor significance, including the CTLA-4 gene, which is important in immune response and predisposes individuals not only to T1D, but also to other autoimmune conditions. Tr. at 152A. Some HLA genotypes confer protection against developing T1D. Eisenbarth, Res. Ex. Q, at 405.

Studies of identical twins indicate that these HLA genes contribute slightly more than 50 percent of the genetic predisposition to T1D. Tr. at 152A. Fathers with T1D are three times more likely to have offspring with T1D than are mothers with T1D. This suggests that mothers may be passing protective antibodies to their offspring. If both parents have T1D, about 25% of their offspring will have T1D. The risk of a child developing T1D is about 9% if the father has T1D and about 3% if the mother has the

[47] Doctor Shoenfeld testified that the concordance rate is 20-30%. Tr. at 57A-59A. However, when Type 1A diabetes is considered separately, the concordance rate for identical twins is 50%. Eisenbarth, Res. Ex. Q, at 403. Another article indicated that the concordance rate depends on the population studied, with rates between 18% and 70% reported. *See* The Institute for Vaccine Safety Diabetes Workshop Panel, *Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety Workshop*, PEDIATR. INFECT. DIS. J. 18(3): 217-22 (1999) ["Vaccine Safety Diabetes Workshop"], filed as Res. Ex. O.

condition. Tr. at 155-58; Res. Ex. TT at 1429.

c. The Role of Autoantibodies.[48]

Doctor Maclaren was involved in the discovery that patients with T1D have antibodies that react to pancreatic islet cells. Later, he helped discover that Type 1 diabetics may produce antibodies (known as "IAA") to insulin itself. One of the antigens discovered by Dr. Maclaren's group is tyrosine phosphatase, called insulinoma antigen 2 or IA2. Groups worldwide collaborated to identify the second major antigen, glutamic acid decarboxylase, known as GAD. Tr. at 153-56.

Autoantibodies usually appear during the first few years of life, years before the clinical symptoms in most patients. The speed at which individuals progress from the presence of antibodies to overt disease is dependent on the age at which the antibodies first appear. Some children develop T1D in early infancy. Some develop T1D in adulthood, more than a decade after the detection of islet cell antibodies. Tr. at 159-62. Some adults do not develop T1D until they are in their 80s. Some never progress to overt clinical symptoms or insulin dependence. What differentiates among these prognoses is not known, although some evidence suggests that an increased number of genes predisposing one to diabetes is found in those with earlier onset. Tr. at 237-39. Clearly, the rate of destruction of β cells is accelerated in those who develop T1D in infancy, and much slower in those who develop T1D in adulthood. Res. Ex. AAA at 2-3; Tr. at 163-64, 237-38.

The natural history of T1D begins with a genetic predisposition, followed by the appearance of the first islet cell antibody, usually during the first nine months to three years of life. Only rarely does someone develop a diabetic autoantibody after age seven. In those that develop one autoantibody, some never develop another. Tr. at 159-60. If someone has not developed antibodies before the age of 10, then the strong likelihood is that he or she will never develop T1D, in spite of genetic predisposition. This is so well established that diabetes prevention trials do not screen individuals over age 20. Tr. at 161.

Based on the discovery of diabetes autoantibodies, Dr. Maclaren's research group screened a large group of relatives of patients with T1D, in order to determine

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[48] There are two kinds of autoantibodies: pathogenic and epiphenomenal. A pathogenic autoantibody is one that causes a disease. Infusing a pathogenic autoantibody into an animal causes the animal to develop the disease. An epiphenominal autoantibody is a marker for a disease process, but does not cause the disease. Transmission of an epiphenominal autoantibody does not transmit the disease. Tr. at 72-73. Although Dr. Shoenfeld testified that there is some slight evidence that the antibodies to GAD are pathogenic (Tr. at 73-77), and he suggested that the nature of the other autoantibodies is uncertain (Tr. at 56-57A), the weight of the evidence is that autoantibodies in T1D are epiphenominal. Tr. at 155-57. The diabetes autoantibody titers appear to be unrelated to the amount of damage to the islet cells or the number of β cells present. Tr. at 272.

when, in the natural history of the condition, the autoantibodies were developed. The group developed an algorithm to predict the onset of T1D, based on the appearance of specific antibodies. The algorithm was validated in a Florida study involving 12,000 school children without any history of diabetes. Of the 12 that ultimately developed T1D, the algorithm predicted the development in eleven of them and in the twelfth, one blood sample was missing. Tr. at 153-55.

Predictive algorithms allow researchers to identify early in life individuals with a genetic susceptibility for development of T1D. By monitoring these individuals closely for the development of autoantibodies and disease onset, the researchers have established the natural course of the development of T1D. Although the levels of autoantibodies have some relationship with the amount of β cell damage, the most important relationship is having more than one antibody. Many individuals develop transient or even persistent low titers of one diabetes autoantibody, and even occasionally high titers, but do not go on to develop T1D. This suggests that the autoantibodies are not pathogenic. However, once more than one autoantibody appears, the likelihood of developing T1D increases immensely. If someone develops two autoantibodies, the likelihood is greater than 90% that the individual will progress to clinical disease within ten years, regardless of the levels of the autoantibodies. Tr. at 153-56, 238-39; Res. Ex. TT at 1430.

This development of more than one autoantibody is referred to as "epitope spreading." Doctor Maclaren testified that once an individual develops two autoantibodies, "it's over," even if the development of the clinically apparent disease takes years. Tr. at 156.

Because islet autoantibodies are difficult to detect, researchers have looked for other methods to measure the slow progression toward insulin dependence. Because glycosylated hemoglobin (HB A_{1c}) levels increase steadily over months or years prior to onset of symptoms, they have become another method of measuring progress toward clinically overt disease. Res. Ex. AAA at 3-4. *See also* Res. Ex. CCC, Tab 10.[49]

d. Other Aspects of T1D Bearing on Prediction and Causality.

Other unique aspects of T1D have played a significant role in the study of the disease, its causes, treatment, and potential cures. Diabetes rates are higher in temperate zones than in the tropics, higher in more industrialized nations than in the developing ones, and higher in Caucasians of northern European descent than in those of African or Asian descent. Res. Ex. TT at 1428. The disease has seasonal

[49] L. Stene, *et al.*, *Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY)*, PEDIATR. DIAB. 7(5): 247-53 (2006). Doctor Rewers was the senior researcher on this study, which showed that increasing HB A_{1c} levels predicted increased risk of progression to clinically overt T1D, independent of the number of autoantibodies.

variability; more cases are diagnosed in late fall or early winter than at any other time.[50] *Id*. In Europe and North America, incidence rates have been increasing at a relatively steady state for over 60 years. While genetic heterogeneity undoubtedly plays a role in the extremely high rates of diabetes found in Finland, Sweden, and Sardinia, genetics alone cannot account for the rising incidence of the disease. Immigrants from areas with low rates of T1D to Europe and North America develop rates of T1D similar to those present in their new country within a generation. Tr. at 225-26.

4. Treatment.

Prior to the development of a process for manufacturing insulin, those who developed T1D died when their bodies could no longer produce enough insulin to sustain life. Treatment of T1D involves injecting insulin several times daily, with the amounts and types (long and short acting insulin) adjusted based on blood glucose readings (spot readings), diet, and exercise levels. It is a chronic condition requiring the lifetime administration of insulin. Pet. Ex. 45 at 3; *see also* Res. Ex. CCC, Tab 1.[51]

Many newly diagnosed diabetics experience a honeymoon phase. As some β cells are destroyed, the remaining β cells work harder to produce insulin. Once T1D is diagnosed and insulin therapy begins, the level of insulin in the blood increases. This eases the burden on the remaining β islet cells, allowing them some level of recovery, although they remain targets for autoimmune destruction. During the honeymoon period, the remaining β cells continue to produce insulin. Therefore, the amount of insulin needed to keep blood glucose low is not as high as it will eventually become. During this honeymoon phase, there is a constant, albeit low, level of insulin being produced and making wide variations in blood glucose less likely. This period can last from a few months to a few years. Tr. at 239-40.

D. Celiac Disease.

Celiac disease is also an autoimmune disorder. It differs from most other autoimmune diseases in that it occurs only when a genetically susceptible individual is exposed to gluten. Tr. at 70. Although celiac disease occurs more often in those with T1D, it is triggered by gliadin, a substance found in gluten, which is unrelated to β cell destruction or insulin production. Exposure to gliadin triggers autoimmunity to

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[50] Type 1 diabetes is most often diagnosed in the fall or winter in the Northern Hemisphere (as in Mr. Hennessey's case) and in late summer or early fall in the Southern Hemisphere. The first appearance of autoantibodies shows a similar seasonal variability. This suggests that some seasonal environmental factor pushes children who are on the brink of insulin dependence over the edge into actual insulin dependence. This seasonal variability is especially evident in school-aged children, but less so in the younger children who have shorter incubation periods. Tr. at 331-32.

[51] M. Rewers, *et al.*, (Diabetes Epidemiology Research International Study Group-DERI), *Trends in the Prevalence and Incidence of Diabetes: Insulin-Dependent Diabetes Mellitus in Childhood*, WORLD HEALTH STAT. Q. 41: 179-89 (1988).

transglutaminase, an enzyme present in the epithelium of the upper intestine. Gliadin triggers an inflammatory response in the upper intestine, with an infiltrate of lymphocytes into the epithelium causing the absorptive villi to become flattened. Tr. at 170B-71.[52] Celiac disease can be treated by eliminating gluten from the diet, allowing the villi to regenerate. Tr. at 171; Eisenbarth, Res. Ex. Q, at 401-02. Tests for celiac autoantibodies in those at genetic risk for T1D and celiac disease demonstrate that autoantibodies to gliadin also appear years before the onset of symptoms. Tr. at 271A.

E. Petitioner's Theories of Causation.

1. In General.

Environmental factors clearly influence which genetically susceptible individuals develop an autoimmune response to β islet cells, starting the lengthy process of destruction of these cells that leads to insulin dependence. Environmental factors must play some role in this process, because the T1D concordance rate between monozygotic twins is not 100%, there are seasonal variations in the incidence rate (suggesting infectious agents or other seasonal factors such as sunlight may play a role), and migration patterns demonstrate an increased incidence of T1D in the first generation of those who immigrate to temperate zones from the tropics. *See generally*, A. Hviid, *et al.*, *Childhood Vaccination and Type 1 Diabetes*, NEJM 350(14): 1398-1402 (2004) ["Hviid"], filed as Res. Ex. CCC, Tab 91 (also filed as Res. Ex. M). The questions presented in this omnibus hearing and in Mr. Hennessey's particular case are: what environmental factors play a role, and are vaccines among them?

Doctor Shoenfeld's expert report and testimony contended that early vaccines (those given in the first months after birth) could, through molecular mimicry, bystander effect, polyclonal activation, or other autoimmune processes, cause the immune system to break tolerance and begin attacking the β islet cells. The viruses, bacteria, preservatives, or adjuvants in these vaccines are all, in his view, potential initiators of the autoimmune process. Tr. at 31A-51. *See generally*, Pet. Ex. 45. This is the direct causation model for a vaccine role in T1D. However, Dr. Shoenfeld acknowledged that his postulated cause and effect relationship between vaccines and T1D conflicted with "the many case-control epidemiological studies that do not show an increased incidence of type I diabetes mellitus following [hepatitis B vaccine] or any other vaccines." Pet. Ex. 45 at 3.

Of course, based on Dr. Shoenfeld's theory, many other environmental factors in the life of an infant, toddler, or child could also initiate an autoimmune process, particularly in a condition with a lengthy prodromal period. The experts were in agreement that the detection of autoantibodies indicates that the β islet cell destruction

[52] Due to an error in the transcript page numbering, the sequential page numbers in this section read "170A," "171A," "170B," and "171."

process is underway. As autoantibodies are usually detected before a child is seven years old,[53] the disease process must begin in utero or in the first years of life. Even if vaccines are among the factors that may initiate the disease process (a proposition by no means established in this evidentiary record), moving them from possible candidates to probable initiators presents significant evidentiary difficulties.[54] *See Munn v. Sec'y, HHS*, 970 F.2d 863, 865 (Fed. Cir. 1992) (noting that "given the vagaries of human illnesses, particularly in young children" proof of vaccine causation is not an easy burden). Because children acquire numerous infections in the first years of life, proving that vaccines are more likely to be causal than these infections is both theoretically and practically difficult. Given the myriad of other possible initiating factors for T1D, the evidentiary burden to demonstrate actual causation could be virtually insurmountable, particularly in view of the numerous epidemiologic studies that have failed to demonstrate any logical connection between vaccines and either T1D or the appearance of β islet cells (discussed in Section III.F.2, below). Perhaps for this reason, Mr. Hennessey has presented a claim focusing on the hepatitis B vaccinations' purported role in the development of clinically overt symptoms.[55] Most of the discussion below, like most of the evidence, concerns the significant aggravation theory.[56]

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[53] Doctor Maclaren testified that the first β islet cell autoantibody usually appears in the first nine months to three years of life. Only rarely does someone develop such antibodies after the age of seven. Tr. at 159.

[54] Doctor Shoenfeld acknowledged that some autoimmune diseases may have long latency periods between trigger and onset, but that the longer the period, the more likely that additional environmental factors could also be causal. Tr. at 53-55.

[55] Although there was some evidence concerning rapid onset in children who develop T1D in infancy, petitioner did not press a rapid induction theory. In view of Mr. Hennessey's age at the appearance of clinical symptoms and Dr. Shoenfeld's testimony that he was probably autoantibody positive at the time of his initial hepatitis B vaccine (Tr. at 65-66), there was no evidentiary support offered for a rapid induction theory. This does not preclude such a theory in other cases in this omnibus grouping where clinical symptoms occurred in early childhood or infancy.

[56] Initially, petitioner's theory for entitlement to compensation in his own case was not clear. Because this was an omnibus test case, evidence was adduced concerning whether vaccines can induce the initial autoimmune reaction resulting in β islet cell destruction, as well as evidence concerning whether vaccines can precipitate or accelerate the onset of insulin dependence. Petitioner's Pre-Hearing Submission did not specify whether Mr. Hennessey's case involved the former, the latter, or both. Petitioner indicated that Dr. Shoenfeld would testify that the hepatitis B vaccine can "induce or accelerate autoimmunity, but only in some individuals." Pet. Pre-hearing Sub. at 10. In the "Legal Analysis" section of his prehearing submission, petitioner both referred to "legal" cause and the significant aggravation of an underlying condition, but failed to clarify whether he was proceeding under either or both theories. Pet. Pre-Hearing Sub. at 14-15. However, in his post-hearing brief, petitioner alleged that the two hepatitis B vaccines he received in the fall of 1998 "caused him to suffer [T1D]." In the next sentence, he acknowledged that the evidence demonstrated a long latency period for T1D, and that "he may have had a subclinical IDDM disease process for years prior to his hep B vaccines...". Pet. Post-Hearing Br. at 1. Based on the uncontroverted evidence of a long prodromal phase in T1D patients who develop the condition at Mr. Hennessey's age, the two hepatitis B vaccines could not have initiated Mr. Hennessey's β cell destruction. As they are the vaccines alleged to be causal, it is now clear that the causation theory

Petitioner relied upon the significant aggravation theory, which builds on a postulated "second hit," advanced to explain why, in the group of people who develop β islet cell autoantibodies, some develop T1D rapidly, some more slowly, and some apparently never do. Tr. at 64A-66, 159-60. What distinguishes early and late onset T1D is not known, but a case-control study that showed a higher incidence of infections in case children than in controls in the three months before onset of clinical symptoms of T1D in the case children[57] suggested that a second triggering event might be necessary in some cases for the development of clinically overt T1D. It is this "second hit" (the first hit being whatever triggered the beginning of the autoimmune attack on the β islet cells) that is implicated in Mr. Hennessey's case, as well as in many of the other cases that are a part of this omnibus proceeding. Under petitioner's significant aggravation theory, any vaccines administered shortly before onset of frank symptoms of diabetes and the beginning of insulin dependence become, in Dr. Shoenfeld's words, "the straw that broke the camel's back" (Tr. at 64A-65), tipping the recipient into insulin dependence.[58] In the context of Mr. Hennessey's individual claim, the significant aggravating factors claimed are the two hepatitis B vaccinations he received in the six to seven weeks before his T1D was diagnosed, which, according to Dr. Shoenfeld, pushed his underlying disease process past the tipping point, making Mr. Hennessey insulin dependent.

Doctor Shoenfeld contended that the epidemiologic studies demonstrating no connection between hepatitis B vaccination and the initiation, or acceleration, of the autoimmune process were inapplicable to Mr. Hennessey's case, and the other T1D cases in which he proffered an opinion favoring vaccine causation, because of the strongly genetic nature of T1D. Thus, he was apparently proposing that some individuals genetically predisposed to developing T1D are also genetically susceptible to certain vaccines, or the adjuvants or preservatives used in the vaccines. Because this would involve "only a few individuals," the effect would be undetectable by epidemiological studies. Pet. Ex. 45 at 4. He also suggested that vitamin D's protective effect was a confounding factor in these epidemiologic studies that cast doubt on their

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alleged is one of significant aggravation.

[57] C. Verge, *et al.*, *Environmental Factors in Childhood IDDM.* DIAB. CARE 17(12): 1381-89 (1994) ["Verge"], filed as Res. Ex. CCC, Tab 37.

[58] Because *Shyface* indicates that petitioners must demonstrate that the vaccine was a "substantial factor" and a "but for" cause of the vaccine injury (165 F.3d at 1352-53), there is an argument that a "straw," added to a multitude of other causes, cannot be considered a "substantial" factor in the development of a condition. Likewise, Dr. Shoenfeld's testimony that Mr. Hennessey was already autoantibody positive, and might well have gone on to develop insulin dependence in the absence of any vaccine (Tr. at 65-67, 82A), suggests that the vaccines were not a "but for" cause of Mr. Hennessey's insulin dependence. However, I need not address this interpretation of *Shyface*, as, even accepting the "straw that broke the camel's back" construction as a substantial factor and a but-for cause of Mr. Hennessey's condition, I find ample factual reasons for rejecting Dr. Shoenfeld's testimony about the causal role of the hepatitis B vaccinations.

conclusions. Tr. at 98A, 122-26.

2. Theories for Autoimmune Responses.

Doctor Shoenfeld offered a number of biologic models or theories to explain how the autoimmune process could begin or accelerate, including a direct attack by a virus on the pancreatic cells,[59] nonspecific tissue damage, bystander effect, polyclonal activation, and molecular mimicry. Most of his testimony and expert report concerned either molecular mimicry or the bystander effect.[60]

The theory of molecular mimicry as the mechanism by which autoimmune diseases occur was first advanced by Dr. Robert Fujinami, and was embraced by Dr. Noel Rose, with whom Dr. Shoenfeld has collaborated on a number of published works. As explained by Dr. Shoenfeld, this theory requires the invasion of the body by a bacteria, virus, or parasite.[61] These invaders contain antigens (proteins) that the host's immune system can recognize. The recognition of an invader signals the immune system to attack the pathogen. Tr. at 33-35.

The immune system is not supposed to recognize the body's own tissue in the same way that it recognizes a foreign invader. During very early development, the immune system develops a tolerance for its own body's tissue because the immune system cells that are capable of recognizing that tissue are eliminated. Tr. at 38A. However, if a foreign protein's molecular sequence resembles a molecular sequence found in the body's own tissue, immune system cells that can recognize both the invading pathogen and, inadvertently, the body's own tissue, may be selected for reproduction in order to fight the invader. Tr. at 36, 114-15. After the invading pathogen has been defeated, these immune system cells may continue the attack, targeting the body's own tissue instead of the invader. This process is sometimes called the "innocent bystander" effect, in that the immune system arsenal continues attacking after the invader is defeated, striking "innocent" host cell tissue.

Doctor Shoenfeld cited several articles as demonstrating molecular mimicry in the development of T1D. Tr. at 110A-14. As the following discussion of these articles

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[59] Doctor Whitton's testimony indicated that a direct viral attack would not be an autoimmune process, nor would an attack by cytotoxic T cells on a virally infected pancreatic cell. Tr. at 448A-49B, 452B-53B. Based on the definition of autoimmunity he provided, I accept Dr. Whitton's testimony as correct.

[60] In examining a possible role for vaccine induction of autoimmune diseases in general, including T1D, the Institute of Medicine called the evidence regarding molecular mimicry as "[t]heoretical only" and for bystander effect "weak." *See* Executive Summary, Table ES-1, IOM Report, 2002. Notwithstanding this report, I set forth Dr. Shoenfeld's testimony on the biological theories in some detail.

[61] Another aspect of Dr. Shoenfeld's theory, that adjuvants or preservatives in vaccines could trigger an autoimmune process, will be discussed further below.

demonstrates, none involved vaccinations or the viruses against which vaccinations are administered.

a. Vaccine Causation of Clinically Overt T1D.

Before the predictive nature of autoantibodies was known and large prospective cohort studies were initiated, most of the studies of the role of vaccines or infections in the development of T1D focused, of necessity, on the appearance of clinically overt symptoms or actual diagnosis of T1D. Doctor Shoenfeld primarily discussed these ecological or retrospective cohort studies in terms of evidence for molecular mimicry at work in the development of T1D. Under Dr. Shoenfeld's formulation of the molecular mimicry theory, if one virus plays a role, then any virus can play a role.

The 1994 Verge article[62] was a case control study conducted in New South Wales, Australia. One of the study's findings was that children with T1D were nearly three times more likely to have experienced an infection in the three months before onset of clinical symptoms, and that this association was stronger in children who were more than nine years of age at the time of diagnosis. The study also found that early introduction of cow's milk formula (before three months of age), day care attendance before the age of three years, and high dietary intake of cow's milk protein in the 12 months before onset of symptoms were all associated with an increased risk of developing T1D. The study also showed that three months or more of exclusive breastfeeding conferred a protective effect. *Id*., Abstract. Doctor Shoenfeld relied on the increased incidence of infection aspect as evidence that molecular mimicry between the infectious agent and the β islet cells caused the autoimmune destruction of such cells. Tr. at 110A-11.

Doctor Shoenfeld also referenced the 1995 Hyoty study,[63] a publication from the Childhood Diabetes in Finland (DiMe) Study Group. The group studied the role of enteroviruses, including Coxsackie B, in the development of T1D. Significantly elevated maternal enterovirus antibodies during pregnancy were linked to the development of T1D in the children, particularly in those whose symptoms manifested before the age of three. Diabetic children with siblings who also had diabetes developed enterovirus infections nearly twice as often as the control children, suggesting a genetic sensitivity to enteroviruses. The increased enterovirus titers were found in these children both close to the time of diagnosis and several years before the diagnosis. Pre-diabetic autoantibodies increased in those with enterovirus infections. However, specimens collected immediately after clinical manifestation of T1D showed no major differences in enterovirus antibodies between patients and the control subjects. *Id*. at 656.

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[62] Verge, Res. Ex. CCC, Tab 37.

[63] H. Hyoty, *et al.*, *A Prospective Study of the Role of Coxsackie B and Other Enterovirus Infections in the Pathogenesis of IDDM*. DIAB. 44(6): 652-57 (1995) ["Hyoty"], filed as Res. Ex. CCC, Tab 41.

The Hyoty study authors observed that enterovirus infections appeared to induce β cell damage both in utero and in childhood. They noted that Coxsackie B viruses (a type of enterovirus) could infect human pancreatic cells in culture, and that IgM antibodies to Coxsackie B virus were found in newly-diagnosed T1D patients, indicating a recent infection. They postulated that either a cytolytic infection of β cells with the virus could facilitate the autoimmune destruction of the β cells or that an epitope in the β cell enzyme GAD was homologous with a protein found in one type of Coxsackie B virus. *Id.* at 656.

A 1995 Lancet article[64] reported similar findings, demonstrating by polymerase chain reaction ["PCR"][65] the presence of enteroviruses in the serum of 64% of children newly diagnosed with T1D, as compared to 4% of the controls. The authors noted that molecular mimicry between a human GAD protein and a Coxsackie virus protein had been proposed as a causal mechanism for induction of β cell autoimmunity.[66] *Id*. at 2.

A role for Epstein-Barr virus in T1D was explored in a 1991 article[67] that Dr. Shoenfeld cited as demonstrating molecular mimicry in T1D. However, in spite of the homology between the Epstein-Barr virus and an HLA associated with autoimmunity and T1D, Epstein-Barr virus antibodies were not found with greater frequency in those with T1D than in non-diabetic controls. The authors concluded that there was "no simple relationship between [Epstein-Barr virus] infections and the homologies and crossreactions which exist between some [Epstein-Barr virus] proteins and class II MHC molecules." Sairenji, Res. Ex. CCC, Tab 47, at 37-38.

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[64] G. Clements and D. Galbraith, *Coxsackie B Virus Infection and Onset of Childhood Diabetes*, LANCET 346(8969): 221-25 (1995), filed as Res. Ex. CCC, Tab 43.

[65] Polymerase chain reaction involves the exponential amplification of genetic material (DNA or RNA that has been converted to DNA ["cDNA"]) by a process that selects sections of gene sequences, induces the DNA to split, and reforms two copies of the original DNA by adding addition of DNA building blocks (bases). For a more detailed explanation of PCR, *see Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044, *110-16 (Fed. Cl. Spec. Mstr. Feb. 12, 2009). "RNA" is an abbreviation for ribonucleic acid. DORLAND'S at 1638. "DNA" is an abbreviation for deoxyribonucleic acid. DORLAND'S at 557.

[66] Doctor Maclaren testified that researchers had demonstrated an 18 amino acid homology between one of the T1D autoantibodies, GAD, and a protein called P2C on the Coxsackie B4 virus, suggesting evidence for molecular mimicry between a virus and islet cells. However, he noted that in the subsequent 15 years, no evidence has developed to show that Coxsackie B virus was associated with the development of islet cell autoantibodies, even in those with the most severe Coxsackie B viral infections. Tr. at 214-18.

[67] T. Sairenji, *et al.*, *Relating homology between the Epstein-Barr virus BOLF1 molecule and HLA-DQw8 β chain to recent onset Type 1(insulin-dependent) diabetes mellitus,* DIABETOL. 34:33-99 (1991) ["Sairenji"], filed as Res. Ex. CCC, Tab 47.

An animal study[68] used a substance that mimics double-stranded viral RNA[69] to explore the process of diabetes induction in transgenic mice. Using polyinosinic-polycytidylic acid ["PolyIC"] and an insulin peptide (B:9-23), the researchers were able to induce insulitis in a type of mice known as BALB/c. They also induced diabetes in mice with created genetic susceptibilities to diabetes, using PolyIC and the same insulin peptide. Interestingly, immunization of the insulin peptide alone or PolyIC alone was sufficient to generate diabetes in some of the genetically susceptible mice. The authors noted that the effect of PolyIC could depend on the dose and time of administration, with low-dose PolyIC preventing diabetes in genetically susceptible rats, and high dose PolyIC accelerating diabetes in the same type of rat. They stated: "It is likely that PolyIC contributes to the induction of insulitis through its effects on the innate immune system. PolyIC is often used as a viral RNA mimic. One can hypothesize that a viral infection with or without a peptide mimicking insulin (or other antigens), with the activation of innate immunity could provide the stimulus for autoimmune β cell destruction in a genetically susceptible host." Moriyama, Res. Ex. CCC, Tab 53, at 5542. Although this study dealt with activation of an autoimmune process, it contained virtually no information suggesting molecular mimicry or bystander effect as the means of initiating the autoimmune process. The connection Dr. Shoenfeld drew was the use of a viral mimic (PolyIC) initiating an autoimmune process (Tr. at 114), rather than anything in a virus mimicking a self-protein.

Doctor Shoenfeld cited to an Italian study[70] examining the role of infectious diseases in onset of T1D, rather than in the initiation of the autoimmune process, and used it to make the argument that if an infection can precipitate the onset of T1D, a vaccine might do so as well. Pet. Ex. 45 at 5-6. The Altobelli study used parental questionnaires completed during the case children's first examination for diabetes and at the control children's next scheduled pediatric examinations to measure the number of infections, both in general and in the year prior to diagnosis or the date of the examination. The total number of infections was not significantly higher in the case children than in the control children, but when the number of recent infections was compared, more than one infection significantly increased the risk of T1D. The odds ratio for two infections was 2.375 and for more than two infections the odds ratio was 6.786. Altobelli, Pet. Ex. 42 at 427. However, vaccination rates were higher in the controls than in the case children, suggesting a protective effect of vaccinations, particularly for pertussis and MMR vaccinations. *Id.* at 428. In contrast to the Wahlberg

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[68] H. Moriyama, *et al.*, *Induction and acceleration of insulitis/diabetes in mice with a viral mimic (polyinosinic-polycyT1Dylic acid) and an insulin self-peptide*. PROC. NATL. ACAD. SCI. 99(8): 5539-44 (2002) ["Moriyama"], filed as Res. Ex. CCC, Tab 53.

[69] Of note, the hepatitis B virus alleged to be causal in this case is a DNA, not an RNA, virus. Tr. at 355A.

[70] E. Altobelli, *et al.*, *Infections and risk of type I diabetes in childhood: A population-based case-control study*, EUR. J. EPIDEMIOL. 18: 425-30 (2003) ["Altobelli"], filed as Pet. Ex. 42.

study, the authors suggested that vaccines may play either a protective or a precipitating role in those at high genetic risk, while noting that literature reviews and a large population based case-control study did not find any effect of immunizations on the incidence of T1D. *Id.* at 429.

b. Vaccine Induction of T1D Autoantibodies.

More recent studies referred to by Dr. Shoenfeld focused on the possible role of infectious agents and vaccines in the development of autoantibodies, instead of, or in addition to, diagnosed T1D. A study[71] by the Finnish Diabetes Prediction and Prevention Study failed to find an association between maternal enterovirus infections and development of T1D in offspring, but did find that enterovirus infections were more frequent in children in the six months preceding the appearance of diabetes autoantibodies than in matched controls.

An association between rotaviruses and β cell autoimmunity was explored in the Honeyman study.[72] The study's authors identified T cell epitope peptides in one T1D autoantibody that appeared to be homologous to one serotype of a rotavirus protein and similar to two other serotypes of the same virus. The study was designed to test their hypothesis that rotavirus infections affect islet autoantibodies in children genetically susceptible to T1D. In the high risk children, three T1D autoantibodies increased with repeated rotavirus infections, most strongly with IA-2Ab, and less strongly with IAA and GAD. There was no evidence that the high risk children had more frequent rotavirus infections. Although Dr. Shoenfeld cited this article as evidence of molecular mimicry in T1D, the authors noted that direct infection of pancreatic islets by rotavirus, rather than an autoimmune attack, was also a plausible explanation for the increased incidence of rotavirus infections in children immediately prior to the development of T1D autoantibodies. As the authors concluded: "The association of IAA, as well as IA-2 and GADab, with [rotavirus] infection could be a consequence of β-cell destruction in susceptible individuals, whether secondary to molecular mimicry, direct infection, or direct pancreatic infection followed by mimicry." *Id*. at 1323.

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[71] M. Lonnrot, *et al.*, *Enterovirus Infection as a Risk Factor for β-cell Autoimmunity in a Prospectively Observed Birth Cohort*, DIAB. 49(8):1314-18 (2000), filed as Res. Ex. CCC, Tab 44.

[72] M. Honeyman, *et al.*, *Association Between Rotavirus Infection and Pancreatic Islet Autoimmunity in Children at Risk of Developing Type 1 Diabetes*, DIAB. 49(8):1319-24 (2000) ["Honeyman"], filed as Res. Ex. CCC, Tab 46.

Doctor Shoenfeld also referred to a study[73] of the humoral (antibody) response[74] to the recombinant hepatitis B vaccine and HLA typing. The study demonstrated varying degrees of humoral response, depending on HLA subtyping, in neonates administered hepatitis B vaccine at birth. Many of the infants who responded poorly to the vaccine had several of the genetic characteristics that predispose a child to T1D, although in one to seven years of followup, none of the genetically predisposed children actually developed T1D autoantibodies. Martinetti, Pet. Ex. 43 at 239. The study's authors drew no conclusion about any causal relationship between the hepatitis B vaccine and T1D, and a careful reading of Dr. Shoenfeld's report (Pet. Ex. 45 at 5-6) discussing this study does not indicate how this study enhanced his theory of causation. That HLA phenotypes may both predispose children to T1D and a failure to respond to the recombinant hepatitis B vaccine does not suggest any causal role between the vaccine and T1D. *Cf. Rotoli v. Sec'y, HHS*, No. 99-644V, 2008 WL 4483739, *12-14 (Fed. Cl. Spec. Mstr. Oct. 2, 2008) (discussing lack of connection between genetic predisposition to fail to respond to hepatitis B vaccine and development of autoimmune hepatitis).

In his report, Dr. Shoenfeld cited to several studies demonstrating the effect of vaccines on the development of autoantibodies, although he did not discuss them during his testimony. Pet. Ex. 45 at 5-6. These included a publication[75] by a Sweden-based study group, ABIS ["All Babies in Southeast Sweden"]. ABIS found an association between two T1D autoantibodies, GAD and IA-2A, at high levels of autoantibody formation (the 90th percentile), and the hemophilus influenzae type B ["Hib"] vaccine and the BCG vaccine[76] (one not given in the U.S.). Vaccine information was derived from parental questionnaires, rather than immunization records, and antibody levels were measured at one year of age. The authors did not conclude that the vaccines were causal of the development of the antibodies, but instead speculated that environmental factors might "have a more pronounced role in the induction of an abnormal immune response in children without high genetic risk...". Wahlberg 2003, Pet. Ex. 41 at 406. They indicated that the Hib vaccine stimulates the immune system, and, thus, might have a polyclonal effect. They planned followup studies to determine if the increased level of autoantibodies had any impact on the development of T1D. *Id.* at

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[73] M. Martinetti, *et al.*, *Humoral Response to Recombinant Hepatitis B Virus Vaccine at Birth: Role of HLA and Beyond*, CLIN. IMMUNOL. 97: 234-40 (2000), filed as Pet. Ex. 43.

[74] The autoimmune destruction of β islet cells in T1D is cell-mediated, not humoral. Doctor Shoenfeld was not clear about how studies measuring antibody response to hepatitis B vaccine apply to a cell-mediated autoantibody reaction.

[75] J. Wahlberg, *et al.*, (ABIS Study Group), *Vaccinations May Induce Diabetes-Related Autoantibodies in One-Year-Old Children*, ANN N. Y. ACAD. SCI. 1005: 404-08 (2003) ["Wahlberg 2003"], filed as Pet. Ex. 41.

[76] "BCG" refers to the bacille Calmette-Guerin vaccine against tuberculosis. Wahlberg 2003, Pet. Ex. 41 at 404-05.

407. No followup studies by this group were filed.

Although there was no evidence adduced that the hepatitis B surface antigen[77] has any homology with the β cell constituents, Dr. Shoenfeld was confident that homology at some level could be found, and that the combination of viral molecules with homology to β cells and adjuvant, injected into mice, would produce diabetes autoantibodies. Tr. at 114-17.

c. Preservatives and Adjuvants as Initiators or Accelerators.

Very little of Dr. Shoenfeld's report or testimony was devoted to what appeared, at least before the hearing, to be the primary focus of petitioner's causation arguments: the role of thimerosal. Without any citations in the body of his report, Dr. Shoenfeld wrote: "Thimerosal is an immunosuppressant as well an agent implicated in autoimmunity." Pet. Ex. 45 at 6.

In Mr. Hennessey's specific case, Dr. Shoenfeld opined that the aluminum adjuvant,[78] the thimerosal preservative, or the hepatitis B surface antigen, singly or together, could have been "the straw that broke the camel's back," pushing Mr. Hennessey into clinically overt T1D. He testified that the first hepatitis B vaccination accelerated the onset of the underlying autoimmune process in Mr. Hennessey, and that administration of the second vaccine caused onset of the disease two weeks later.[79] Tr. at 64A-65. Doctor Shoenfeld variously opined that, without the hepatitis B vaccines, Mr. Hennessey might either have developed T1D anyway or the underlying

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[77] The hepatitis B vaccine differs from most other childhood immunizations in that it contains no infectious agent. Most vaccines contain killed bacteria, live attenuated viruses, or toxins which induce an immune system response. Unlike these vaccines, the hepatitis B vaccine in general use in the U.S. (including the vaccines received by Mr. Hennessey), did not contain any part of the hepatitis B virus. It is a recombinant vaccine containing a protein derived from a hepatitis B surface antigen (proteins expressed on the surface of a virus capable of being recognized by immune system components) and produced in yeast cells. This antigen was inserted into a DNA plasmid. As the antigen is the part of the virus the immune system recognizes, the DNA plasmids displaying the antigen trigger the immune system to respond. Aluminum adjuvants are necessary in this vaccine to stimulate the immune system to respond appropriately because no actual hepatitis B virus is present, and the protein alone cannot induce a strong CD8 (cytotoxic or killer) T cell response. Even with the adjuvant, the vaccine is less effective in inducing an immune system response than the virus itself. The vaccine stimulates a CD4 (T-helper cell) response and an antibody response, but is poor at stimulating a CD8 T cell response. Res. Exs. RR at 6 and AAA at 11; Tr. at 46-48, 371A-73A.

[78] I note that one of Dr. Shoenfeld's cited articles, L. Levitsky, *Childhood Immunizations and Chronic Illness*, NEJM 350(14):1380-82 (2004), filed as Pet. Ex. 44, indicated that "the aluminum burden in vaccines is lower than that found in breast milk or formula." *Id*. at 2-3. Doctor Shoenfeld did not specifically cite to any study demonstrating a role for aluminum in T1D.

[79] Although Mr. Hennessey's T1D was diagnosed two weeks after his second hepatitis B vaccine, both the medical records and his mother's affidavit place onset of clear symptoms two days after the second vaccination.

disease process might have arrested, since not everyone who has autoantibodies goes on to develop clinically overt T1D. Tr. at 65-66, 86. He conceded that Mr. Hennessey likely had diabetes autoantibodies at the time he received his hepatitis B vaccinations. However, he testified that the vaccinations aggravated the preexisting disease process and hastened the onset of the clinically overt disease. Tr. at 65-67, 82A.

Under cross-examination, Dr. Shoenfeld conceded that it was generally safe for patients with autoimmune disease to be vaccinated, but noted that some autoantibody levels increase in autoimmune disease patients after vaccination. Tr. at 100-101. Had he known that Mr. Hennessey had diabetes autoantibodies, he would have advised him to "[a]void any vaccine not deemed necessary." Tr. at 102-03.

The term "bystander effect" describes a theory of autoimmunity that involves something inducing a change in the body's own cells that renders them "recognizable" by the immune system. Doctor Shoenfeld suggested that mercury from the thimerosal preservative once used in many vaccines could cause such an effect. According to Dr. Shoenfeld, mercury is one of many chemicals that can modulate the ports of entry to a cell, creating antigens on the cell's surface that can be recognized by the immune system and causing the immune system to treat that cell as a foreign invader. Tr. at 35, 39-41. He indicated that the individual response to mercury, arsenic, and other chemicals varies from individual to individual, making some individuals more susceptible than others to mercury's effects. However, he did not point to any evidence for hypersusceptibility in Mr. Hennessey in particular, or in those with T1D in general. He also stated that thimerosal could modulate an infectious agent, such as the surface antigen to the hepatitis B virus used in the hepatitis B vaccine, making it more infectious. Doctor Shoenfeld also testified that the aluminum adjuvant used in the hepatitis B vaccine could enhance an autoimmune reaction already underway, as well as induce an autoimmune reaction itself. Tr. at 47-48.

d. The Theory in Summary.

Doctor Shoenfeld proposed several permutations to his general theories of what triggers autoimmune diseases to explain why he believed vaccines could be causal, or an accelerator, of autoimmune destruction of β islet cells. According to Dr. Shoenfeld, vaccines administered in childhood may make someone prone to develop an autoimmune disease or more prone to react in an autoimmune manner to subsequent vaccines. Tr. at 64A-65. Given that T1D is a disease with a slow incubation period, vaccines may also supply the "second hit." He testified that a vaccine may accelerate the onset of clinical disease, and a second vaccine may, within a short period after the first, trigger the onset of full-blown disease. Tr. at 54, 67-68.

Doctor Shoenfeld asserted that congenital rubella could cause T1D, as could rotoviruses, enteroviruses, Epstein-Barr, hepatitis B and Coxsackie B viruses. An accumulation of infections can cause autoimmune diseases as well. Tr. at 43-44, 61-62. He added that if an infection can cause a disease, a vaccine can cause it, and

testified that the viral envelope may be what triggers autoimmunity, rather than the viral proteins inside that envelope, apparently referring to the hepatitis B surface antigen. Tr. at 46. He was of the opinion that, as T1D is an autoimmune disease, potentially any vaccine could cause it. Tr. at 81.

Other than a role for congenital rubella, and possibly enteroviruses, respondent's experts hotly contested Dr. Shoenfeld's assertions about viral causation of either the development of autoantibodies or accelerated onset of clinically overt disease. They also took exception to Dr. Shoenfeld's opinion that any vaccine could be causal of T1D. In doing so, they directly and indirectly challenged his reliance on the molecular mimicry theory, but the primary focus of their arguments was on the lack of evidence supporting any logical connection between the theory and T1D, and the wealth of evidence that vaccines are not causal. Their opinions are addressed, *infra.*

3. Causation of Celiac Disease.

Although his report stated that the "development of celiac disease is a known complication associated with T1D," suggesting a causal relationship between T1D and celiac disease, Dr. Shoenfeld testified it was uncertain if Mr. Hennessey's celiac disease was a direct consequence of his vaccines. Pet. Ex. 45 at 7; Tr. at 69-71, 119. He did not opine that the vaccines were likely or probably causal of celiac disease. Thus, his testimony about vaccine causation of Mr. Hennessey's celiac disease falls short of what is necessary to prove vaccine causation. At best, Dr. Shoenfeld's testimony and report suggest that whatever caused Mr. Hennessey's T1D also led to the development of his celiac disease. If Mr. Hennessey cannot demonstrate by preponderant evidence that vaccines caused his T1D, he cannot demonstrate their causal role in his celiac disease.

F. Evidence Rebutting Vaccine Causation.

1. In General.

Childhood diabetes has been the subject of intense study in Europe and North America for decades. Studies have identified both genetic susceptibilities and environmental risk factors, although the evidence concerning risk factors has been conflicting, perhaps because of the difficulty in accounting for confounding factors and recall biases in most of the ecological and case-control studies. Several long-term cohort studies have enhanced efforts to determine how to prevent the development of autoantibodies in the first instance, and develop treatments to "turn off," or slow down, the autoimmune process once the first autoantibodies appear. Doctor Rewers has

played a key role in the two largest U.S. prospective cohort studies, DAISY[80] and TEDDY.[81]

Respondent's experts persuasively testified that there is no evidence that vaccines play any role in initiating the autoimmune process or in supplying the sometimes-postulated "second hit" that pushes an individual into insulin dependence. Each of respondent's three experts addressed specific aspects of Dr. Shoenfeld's report and testimony.

Doctor Maclaren provided much of the background information on the natural history of T1D addressed earlier in this opinion. He also testified about the significance of diagnostic tests and Mr. Hennessey's symptoms. Based on his 30 years of experience as a researcher and clinician in T1D, he persuasively opined that, at the time Mr. Hennessey received his initial hepatitis B vaccination, he was already experiencing subtle clinical symptoms of diabetes, with those symptoms becoming more obvious at the time of, or very shortly after, the second hepatitis B vaccination. More significantly, he opined that, based on laboratory evidence, Mr. Hennessey's blood glucose levels at the time of his first hepatitis B vaccination were high enough to meet the diagnostic criteria for T1D before he received that vaccination.

Doctor Rewers, who currently heads major, long-term studies into T1D's causes and potential treatments, provided a wealth of information about what recent studies have revealed. Doctor Rewers characterized his role in DAISY and TEDDY, two of the major studies, as moving candidate risk factors from the list of possible causes of T1D to a list of probable causes. Tr. at 267. He also buttressed Dr. Maclaren's testimony that Mr. Hennessey's clinical presentation was inconsistent with hepatitis B vaccination precipitating his insulin dependence.

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[80] "DAISY" stands for "Diabetes Auto Immunity Study in the Young." Tr. at 248. This prospective cohort study, which began in 1993 and is still in process, began by genetically screening over 30,000 babies, born to families with a history of T1D, for genetic susceptibility to T1D. *See, e.g.*, Res. Ex. CCC, Tab 6.

[81] "TEDDY" stands for "The Environmental Determinants of Diabetes in the Young." *See* Res. Ex. C, *Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan* ["NIH T1D Strategic Plan"] (developed under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee), found at *www.T1Diabetes.nih.gov/plan.* This is the National Institute of Health's strategic plan for diabetes research efforts, part of which includes TEDDY. The DAISY project generated interest in a similar study in Europe and a broader study within the U.S, leading to the design and funding of TEDDY, which involves research centers in Finland, Sweden, and Germany in Europe, and in Georgia, Florida, and Washington in the U.S. The study is focused on finding the environmental determinants of T1D by screening 350,000 newborns and following 8,000 of those at high genetic risk for up to 15 years. Doctor Rewers is the co-chair of the steering committee for TEDDY. Tr. at 249-50.

Doctor Whitton, with outstanding credentials in immunology, virology, autoimmunity, and vaccines (see Res. Ex. Y) offered incisive critiques of Dr. Shoenfeld's theories of autoimmunity relating to vaccine causation, as well as cogently explaining the theories themselves. Tr. at 374A-77; 382-393A.

2. Evidence Rebutting Petitioner's Theories Regarding T1D and Vaccines.

a. Epidemiologic Studies Indicate Vaccines are Unlikely as a Cause of T1D.

Most of the testimony concerning epidemiology was supplied by Dr. Rewers. Given his extraordinary credentials in both pediatric endocrinology and epidemiology, his specific research focus on the causes of T1D, and his lucid and highly compelling testimony, I placed great reliance on the evidence he supplied.

(1) Epidemiology in General.

Doctor Rewers testified that he viewed the role of epidemiologic studies of T1D as helping scientists to move candidate causal agents from possible causes, to probable causes, or even to definitive causes. He acknowledged the inherent weaknesses in epidemiology, but noted that when many studies have examined the same hypothesis, with consistent results, the probability that those results are correct is significantly enhanced. Tr. at 267, 329-30. As he testified: "We are reassured that none of the vaccines that we have so far looked at has an association with either development of islet autoantibodies or clinical diabetes." Tr. at 301.

Doctor Rewers explained the various types of epidemiologic studies that have looked for T1D's causes. In his opinion, the best type of study is the clinical trial, but clinical trials cannot be used to test some hypotheses regarding T1D causation, because some of the candidate causal agents, such as enteroviruses, are harmful. However, some hypotheses regarding T1D developed in other types of epidemiologic studies have been tested in clinical trials. Tr. at 329-30.

An ecological study is the simplest type of epidemiologic study available. This type of study compares two or more trends. For example, an ecological study of the rising incidence of T1D since 1950 might show a curve similar to the rise in the number of cars, televisions, or microwave ovens over the same period, trends that are not likely to be causally related to T1D (or to each other). Comparable curves cannot be related in a causal way until the exposure levels of children with T1D are compared to similar children without T1D, known as controls. Case-control studies involve this comparison of potential risk factors in populations with and without the condition. Because case-control studies are retrospective in nature, they are prone to selection bias. Tr. at 284, 326-28. When they are based on recall of events occurring years earlier, they are also prone to recall bias.

Thus, if ecological studies suggested a possible connection between vaccines and T1D, a case-control study could test whether the connection was causal or merely coincidental. This case-control study would compare vaccine coverage rates in children with and without T1D. If a higher proportion of the children with T1D had received vaccines than the proportion of the control children, the case-control study would be some evidence of a causal connection. To illustrate, if 60% of the case children (those with T1D) received Vaccine A, the odds of receiving the vaccine would be 1.5.[82] If, in the control group (composed of children who do not have T1D), only 50% of the children received the vaccine, the odds ratio for the control children would be 1. A comparison of the two odds ratios might suggest that Vaccine A could play a causal role. Doctor Rewers noted that odds ratios themselves are not significant unless the confidence interval[83] does not include 1. Tr. at 284-85A.

Although Dr. Shoenfeld testified that case-control studies are not a good method for studying rare diseases,[84] Dr. Rewers disagreed, testifying that such studies are often the best option for quickly studying an uncommon disease. Tr. at 328. I credit Dr. Rewers' testimony over that of Dr. Shoenfeld on this point, based not only on his much greater experience in epidemiology (and the epidemiology of T1D, a rare disease), but also because of the many case-control studies of T1D. Many of these studies compared vaccine coverage for large numbers of children with T1D to a large number of children without the disease, and, thus, have sufficient power to detect causal factors.

Cohort studies are more precise than case control studies, because they are prospective in nature. Over a period of years, they may find that small levels of exposure have an effect. Doctor Rewers' example was a cohort study that lasted 20-30 years and which demonstrated that small changes in cholesterol levels are harmful to the heart. Tr. at 328. DAISY[85] and TEDDY are both long-term cohort studies;

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[82] This odds ratio is computed by comparing, in the children with T1D, the odds of getting the vaccine (60%) to the odds of not getting the vaccine (40%), dividing 60 by 40, with an answer of 1.5.

[83] A confidence interval that encompasses 1 means that the odds ratio is not statistically significant. Tr. at 294A-95A.

[84] I note that one of the studies cited by Dr. Shoenfeld in support of vaccine causation, Altobelli, Pet. Ex. 42, was a population based case-control study, whose authors stated that such studies were generally considered suitable for the study of rare diseases, such as T1D. *Id*. at 428-29.

[85] The DAISY cohort was selected based on tests of cord blood samples from over 30,000 babies for HLA DR-DQ markers, which indicate a propensity to develop T1D. Ten percent of those at the highest level of genetic risk were enrolled in the study, a total of 1411 babies. Additionally 1058 babies or children from families in which a parent or older sibling had T1D were also enrolled. Tr. at 260-62. After the initial HLA typing, the infants had blood drawn at nine, 15, and 24 months of age. If the infants remained negative for prediabetic autoantibodies at 24 months of age, they were seen annually thereafter. If they were positive for any of the diabetic autoantibodies, including GAD, IAA, IA-2, and ZnT8, the infants were screened every three to six months. In addition to testing for diabetes autoantibodies, the study measured

moreover, because these studies select children with high genetic risk for T1D, they can enroll smaller numbers of children than most other studies of rare conditions.[86]

Repeated studies are important because they allow for multiple comparisons of risk factors to be identified or ruled out. Because there are many studies of causal factors in T1D, when the majority of the studies identify or reject an environmental exposure as a risk factor, their findings carry significant weight. Tr. at 290A.

(2) The Epidemiologic Search for Causes.

As the epidemiologic studies discussed by Dr. Shoenfeld indicated, various viral or bacterial pathogens were considered possible causal factors in T1D. Since many, but not all, vaccines contain infectious agents,[87] albeit in a killed or attenuated form, vaccines were also considered as possible causes. Epidemiologic studies have examined the role of vaccines in the development of clinically overt disease, and, more recently, whether they play a role in the initiation of diabetes autoantibodies. The well-conducted studies, both in the U.S. and in Europe, have failed to find any link. The data developed in DAISY do not indicate that infections trigger the onset of diabetes autoantibodies. Tr. at 275. The epidemiologic studies filed and discussed also indicated that vaccines are not likely candidates as initiators of overt clinical symptoms.

Early studies, including most of those mentioned by Dr. Shoenfeld in his report and testimony, examined vaccinations, early and recent infections, and drugs as possible risk determinants in T1D. Noting that viral inducement of T1D had been suspected for more than a century, a group of researchers at the Karolinska Institute in

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levels of viral antibodies and, using PCR technology, looked for the actual viruses (as opposed to viral antibodies) in throat, stool or rectal swabs, saliva and blood. The research clinic also tracked information on immunization status, diet, infections, attendance at day care and other postulated risk factors for T1D. Tr. at 248, 262-64; Res. Tr. Ex. 2, p. 3. The study measured vitamin D levels and included detailed dietary and nutritional information on vitamin D intake and supplements of both the children and the mothers during pregnancy. Tr. at 266-67.

[86] Cohort studies of rare conditions are ordinarily quite difficult to do because of the extremely large numbers of participants required in order to find, over time, enough "cases" for valid comparisons. To illustrate, if a condition is found in only 1% of the population, a prospective cohort study would need to enroll 10,000 participants in order to obtain 100 individuals with the condition under study. Such a study would be extremely expensive. If, through genetic screening, a population with an increased genetic risk can be identified, the number of enrolled participants can be greatly reduced, while still producing enough cases of the condition for study.

[87] The hepatitis B vaccine does not contain any infectious agents or particles (Tr. at 371A), the many references in Dr. Shoenfeld's testimony detailed in petitioner's post-hearing reply brief (*see, e.g.* Pet. Reply to Respondent's Post-Hearing Submission at 7) to such "infectious" content notwithstanding.

Sweden published a study[88] in 1991 that examined risk factors. All children in Sweden who were diagnosed with T1D between September 1985 and August 1986 were matched with two controls. Families of both case and control children answered questionnaires about recent illnesses, childhood diseases, and vaccinations. Vaccination records were also obtained. The diabetic children reported more frequent respiratory and ear infections in the year preceding their diagnosis. The diabetic children had a slightly smaller number of gastrointestinal infections during their first year of life. Vaccination status was not a risk factor; in fact, both the monovalent measles vaccination and the MMR vaccination appeared to have a protective effect. Overall medication use did not vary significantly between the two groups, although the diabetic children had a higher use of antibiotics, analgesics, and antipyretics in the year prior to T1D diagnosis.

Many case-control studies, like the Blom study (Res. Ex. CCC, Tab 88), had a common weakness in that they relied upon parental interviews and memories from years after the events in question to record the dietary and other environmental factors for study. One study[89] cast considerable doubt on the reliability of parental recall after a period of years. Reliance on parental recall to determine risk factors in T1D can be illustrated by comparing a retrospective study with a prospective one. A meta-analysis[90] of retrospective studies of dietary risk factors indicated that early exposure to cow's milk was a large risk factor in the development of T1D.[91] Another meta-analysis[92] examined the underlying studies more critically for the possibility of recall bias, and determined that studies using infant records to assess duration of breastfeeding failed to show the same association between cow's milk and T1D found in studies relying on long-term parental recall data. In comparison, a DAISY study using prospectively collected records did not

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[88] L. Blom, *et al.*, *The Swedish childhood diabetes study: Vaccinations and infections as risk determinants for diabetes in childhood,* DIABETOL. 34: 176-81 (1991) ["Blom"], filed as Res. Ex. CCC, Tab 88.

[89] J. Vobecky, *et al.*, *The Reliability of the Maternal Memory in a Retrospective Assessment of Nutritional Status*, J. CLIN. EPIDEMIOL. 41: 261-65 (1988) ["Vobecky"], filed as Res. Ex. CCC, Tab 18. This study compared nutritional data (duration of breastfeeding, age at introduction of solid food, and age at introduction of meat), gathered contemporaneously in the first year of life, with maternal recall of the same data eight years later. The study found that the mothers tended to over- or under-report the age at introduction of solid foods and the duration of breastfeeding, when questioned years after these events.

[90] A meta-analysis aggregates data from several similar studies. If similar trends are found, the reliance placed on the conclusions is enhanced. Tr. 295A-96A.

[91] H. Gerstein, *Cow's Milk Exposure and Type I Diabetes Mellitus - A critical overview of the clinical literature*, DIAB. CARE 17(1):13-18 (1994), filed as Res. Ex. CCC, Tab 17.

[92] J. Norris and F. Scott, *A Meta-Analysis of Infant Diet and Insulin-Dependent Diabetes Mellitus: Do Biases Play a Role?* EPIDEMIOLOGY 7(1): 87-92 (1996), filed as Res. Ex. CCC, Tab 19.

find any association between length of breastfeeding and T1D.[93]

Many of the more recent studies looking for a possible connection between vaccines and T1D had their impetus in the 1997 publication of an article[94] purportedly finding a link between vaccines, the timing of vaccines, and T1D. This 1997 publication by David and John Classen formed the basis for the petitioners' T1D claims in *Baker*, 2003 U.S. Claims LEXIS 290. This study suggested that some vaccines given after the age of two months increased the risk of T1D. It noted a "clustering" of T1D diagnoses three to four years after specific vaccinations.[95] Classen, Res. Ex. CCC, at 452-53. These theories and findings were extensively criticized in the medical literature and by respondent's experts in *Baker*.[96] Many of the studies of possible vaccine causation of T1D, filed in the instant case, cited to the Classen study and then proceeded to

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[93] J. Norris, *et al.*, *Lack of Association Between Early Exposure to Cow's Milk Protein and β-Cell Autoimmunity (DAISY)*, JAMA 276(8): 609-14 (1996), filed as Res. Ex. CCC, Tab 23. *See also* P. Graves, *et al.*, *Lack of Association Between Early Childhood Immunizations and β-Cell Autoimmunity,* DIAB. CARE 22(10): 1694-97 (1999) ["Graves"], filed as Res. Ex. CCC, Tab 99 .

[94] D. Classen and J. Classen, *The Timing of Pediatric Immunization and the Risk of Insulin-Dependent Diabetes Mellitus,* INFECT. DIS. CLIN. PRACT. 6: 449-54 (1997) ["Classen"], filed as Res. Ex. CCC, Tab 86.

[95] Doctor Classen's conclusions were drawn, at least in part, from animal studies. The Classen article, Res. Ex. CCC, Tab 86, reported on earlier work by Dr. Classen, which demonstrated that the administration of DTP and anthrax vaccines to nonobese diabetic ["NOD"] mice and BioBreeding ["BB"] rats at birth prevented the development of diabetes, but that administration of the DPT vaccine at eight weeks of age in these rodents was associated with an increased incidence of diabetes. *Id*. at 449. *See also* F. DeStefano, *et al.*, *Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus*, PEDIATRICS 108(6): 1-5 (2001) ["DeStefano"], filed as Res. Ex. CCC, Tab 92 at 4-5 (noting Classen's reliance on animal studies). As Dr. Maclaren explained, two very inbred rodents, the BB rat and the NOD mouse, have proven extremely useful in the study of T1D, but they are not complete analogs for human beings. Some substances that induce or prevent T1D in these animals do not appear to have a similar effect in humans. In NOD mice, daily doses of insulin resulted in dramatically lower diabetes rates. However, in a large NIH trial of this therapy in humans, there was no evidence that insulin had a protective effect. Tr. at 186-88. Freund's complete adjuvant has a protective effect against diabetes in BB rats, and the BCG vaccine protects NOD mice against diabetes, but studies have not shown any similar effect in humans. Tr. at 223-25.

[96] *See generally,* Baker, 2003 U.S. Claims LEXIS 290 (extensively reviewing criticisms of Dr. Classen's research). Doctor Rewers' testimony echoed many of the same criticisms of Dr. Classen's work covered in the *Baker* decision. He noted that Dr. Classen's work on vaccines and T1D had been thoroughly discredited and that Dr. Classen had a financial interest in finding a relationship between vaccine timing and the development of T1D, having filed a patent for a new vaccine administration schedule. Finally, Dr. Rewers commented on Dr. Classen's penchant for reanalyzing data from other studies to find a T1D-vaccine relationship, commenting that the original researchers in one such attempt called Dr. Classen's reanalysis nonsense. Tr. at 310A.

contradict or criticize it.[97]

The Classen study's hypotheses provided the impetus for a large workshop involving epidemiologists, endocrinologists, and others[98] at Johns Hopkins School of Public Health in March, 1998. The results of the workshop were reported in March, 1999. *See* Vaccine Safety Workshop, Res. Ex. CCC, Tab 98, at 4-5 (using the page numbers appearing in the upper right hand corner of each page). The workshop report directly addressed Dr. Classen's data and hypotheses, noting the numerous other studies that contradicted them, and commented that, with regard to unpublished data from a Finnish study cited by Dr. Classen, his "analytic methods were incorrect." *Id.* at 5.

More recent studies, similar to the model developed in DAISY,[99] are collecting data on environmental exposures, either prospectively, or closer in time to the actual events studied. Dietary factors, environmental toxins, specific viruses, the "hygiene hypothesis," congenital exposures,[100] and vaccines have all been examined in epidemiologic studies. The strongest data regarding causation to come from the DAISY study are in the area of nutrition. A 2003 article[101] discussed one significant nutritional finding. In children with a high genetic risk for T1D, those who were given cereal prior to four months of age or after six months of age were at a greater risk of developing diabetes autoantibodies, compared to children whose first exposure to cereal occurred between four and six months of age. This finding may be limited to those haplotypes

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[97] *See, e.g.*, T. Vial and J. Descotes, *Autoimmune diseases and vaccinations*, EUR. J. DERMATOL. 14: 86-90 (2004), filed as Pet. Ex. 40, and Graves, Res. Ex. CCC, Tab 99. The first three hypotheses tested in the Graves study, which was based on DAISY data, were those advanced by Dr. Classen. The study conclusively refuted them. The authors noted that Dr. Classen's hypotheses had received significant publicity, causing concern among parents. *Id.* at 1694.

[98] Doctor John Classen was one of the workshop participants. Vaccine Safety Workshop, Res. Ex. CCC, Tab 98. The participants are listed at the end of the article.

[99] These include the Germany "BABYDIAB" study (*see* U. Roll, *et al.*, *Perinatal Autoimmunity in Offspring of Diabetic Parents. The German Multi-Center BABY-DIAB Study: Detection of Humoral Immune Responses to Islet Antigens in Early Childhood*, DIAB. 45: 967-73 (1996), filed as Res. Ex. CCC, Tab 7 (describing the German prospective study population) and the "EURODIAB" study (*see* EURODIAB Substudy 2 Study Group, *Vitamin D supplement in early childhood and risk for Type 1 (insulin-dependent) diabetes mellitus*, DIABETOL. 42: 51-54 (1999) ["EURODIAB"], filed as Res. Ex. CCC, Tab 31).

[100] *See* L. Stene, *et al.*, *Symptoms of Common Maternal Infections in Pregnancy and Risk of Islet Autoimmunity in Early Childhood*, DIAB. CARE 26(11): 3136-41 (2003) ["Stene 2003"], filed as Res. Ex. CCC, Tab 67. This DAISY study examined maternal infections during pregnancy, neonatal infections, daycare attendance, exposure to pets, and household crowding in early childhood as possible risk factors for T1D. Maternal symptoms of infections during pregnancy predicted a significantly lower risk of developing T1D autoantibodies in daughters, but not in sons. *Id*. at 3136.

[101] J. Norris, *et al.*, *Timing of Initial Cereal Exposure in Infancy and Risk of Islet Autoimmunity*, JAMA, 290(13): 1713-20 (2003) ["Norris 2003"], filed as Res. Ex. CCC, Tab 28. Doctor Rewers was listed as the senior researcher on this article.

types of T1D that share a susceptibility to celiac disease. Tr. at 274A-76; Norris 2003, Res. Ex. CCC, Tab 28, at 1720. Low intake of omega fatty acids also appears to be a risk factor. Tr. at 275-76.

Some infections, including maternal infections during pregnancy, appear to have a protective effect, leading to the "hygiene hypothesis"[102] for T1D causation (*see* Stene 2003, Res. Ex. CCC, Tab 67), although the evidence for this hypothesis is still conflicting. A meta-analysis found lower risk of T1D in children who attend day care centers early in life,[103] but the prospective DAISY data did not find any protective effect from day care attendance.[104]

Doctor Shoenfeld testified that vitamin D can slow down the disease process or even prevent autoimmune disease. Tr. at 30 (page unnumbered), 128-31. He did not specify whether it was effective in either preventing or slowing the β islet cell destruction in the prodromal phase of T1D. Although he referred to a 2007 study (Tr. at 122), it was never filed. However, several articles in Dr. Rewers' references addressed the protective effect of vitamin D.[105] Contrary to Dr. Shoenfeld's assertions that the epidemiologic

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[102] The "hygiene hypothesis" suggests that increased hygiene standards in developed countries mean that children are exposed to fewer pathogens, and thus their immune systems are not sufficiently challenged, leading to the development of allergic diseases. 2002 IOM Report, Res. Ex. L, at 6-7. The hygiene hypothesis in T1D and other autoimmune diseases is based on the increase in autoimmune diseases since the 1950s, combined with the decrease in the number of infectious diseases experienced during the same period. A possible cause and effect relationship between the two is speculative, but intriguing, according to Dr. Maclaren. He noted that the T1D rate in India is very low, while the rate of those exposed to the bacteria that cause leprosy is very high. However, the children of Indians who emigrate to the U.S. or the U.K. have a rate of T1D similar to that of the general population in both countries, suggesting that Indians have the genetic risk for T1D, but that something in the Indian environment is protective. Tr. at 224-26.

[103] Day care center attendance is a surrogate measure of the number of infections, as children who attend day care are exposed to a greater number of pathogens, based on their proximity to many other children. *See* B. Kaila and S. Taback, *The Effect of Day Care Exposure on the Risk of Developing Type 1 Diabetes*, DIAB. CARE 24(8): 1353-58 (2001), filed as Res. Ex. CCC, Tab. 63. The authors noted that several well-designed case-control studies showed a protective effect of day care, but the heterogeneity in the studies, coupled with the retrospective reporting, militated against accepting this finding. The authors recommended that a prospective study be conducted, which was done in DAISY.

[104] Stene 2003, Res. Ex. CCC, Tab 67. According to this DAISY study, early day care attendance, as well as household crowding and exposure to household pets, did not affect the development of β islet autoimmunity.

[105] *See* E. Hypponen, *et al.*, *Intake of vitamin D and risk of type 1 diabetes: a birth cohort study,* LANCET 358: 1500-03 (2001) ["Hypponen"], filed as Res. Ex. CCC, Tab 30 and L. Stene, *Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study*, AM. J. CLIN. NUTR. 78: 1128-34 (2003) ["Stene 2003a"], filed as Res. Ex. CCC, Tab 33. The 2001 Hypponen study was based on data from Finland and found a protective effect of vitamin D supplementation during the first year of life in one cohort of children born in 1986. The 2003a Stene study was a nationwide case-control study in Norway that concluded, after adjusting for a

studies did not account for the confounding effect of vitamin D intake, Dr. Rewers testified that the DAISY study measured vitamin D levels and included detailed dietary and nutritional information on vitamin D intake and supplements for both the children and the mothers during pregnancy. Tr. at 266-27.

The prior publication of studies on vitamin D and the DAISY study's collection of information on vitamin D levels is significant for two reasons. First, the European studies, published in 1999, 2001, and 2003 (discussed in n. 106, below) consistently found that vitamin D supplementation in the first year of life conferred some degree of protection against developing T1D. Doctor Shoenfeld testified about his research facility's examination of vitamin D's role in preventing other autoimmune diseases (Tr. at 122-24), indicating that this was a new finding. Second, he asserted that his recent acquisition of information about vitamin D's protective effect accounted, at least in part, for his change of opinion between his written work and his trial testimony and report regarding the likelihood that vaccines play a role in the development of T1D. He explained that the epidemiologic studies finding no relationship between T1D and vaccinations did not control for vitamin D levels and that the failure to do so was a confounder that might render the studies' conclusions invalid. Tr. at 98A-99, 121, 129-32. Although Dr. Shoenfeld's testimony strongly suggested that the protective effect of vitamin D was "new evidence," the dates of these studies and the consistency of their findings, at least with regard to infant supplementation, indicated that the effect of vitamin D had been known for years. Thus, Dr. Shoenfeld's dismissal at the hearing of epidemiological studies of vaccinations and T1D (studies he previously called "well-conducted"), because they did not consider vitamin D intake as a possible confounder, does not appear to be valid. Furthermore, in the prospective studies (*e.g.*, DAISY or TEDDY), the children enrolled were from the same geographic area,[106] and Dr. Shoenfeld advanced no reason for assuming that vitamin D intake would differ based on vaccination status.

Given the suspicion that infections may either initiate the autoimmune process or trigger the onset of insulin dependence, a number of studies have examined the possible role of vaccines in both events. All of the well-conducted epidemiologic

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number of potential confounding factors, that cod liver oil (containing vitamin D), administered during the first year of life, was associated with a significantly lower risk of T1D. *See also* Res. Ex. CCC, Tab 31, the EURODIAB Vitamin D study. Noting the north-south gradient in cases of T1D (more cases in northern latitudes than in southern latitudes within Europe and within Sweden), this study examined whether vitamin D supplementation affected T1D rates within seven countries in Europe. It concluded that supplementation in infancy decreased the risk of T1D, regardless of geography or other potential confounding factors.

[106] *See, e.g.*, Graves, Res. Ex. CCC, Tab 99. Geography may affect sunlight exposure, which also affects vitamin D production.

studies[107] have failed to find any relationship between vaccines and the onset of T1D. The robust investigations of the vaccine-T1D hypothesis led the Institute of Medicine to reject any "causal relationship between multiple immunizations and the risk of T1D."[108]

In contrast to the findings of the retrospective Wahlberg study, Pet. Ex. 41, the German BABYDIAB study failed to detect any effect from either the type (including BCG, tick-borne encephalitis, Hib, DTaP, polio, and MMR vaccines) or the quantity of vaccinations on islet autoimmunity.[109] Although this study included some vaccines not given in the U.S. (BCG and tick-borne encephalitis), these particular vaccines were received by only a small number of the children in the study. The study found that autoantibody-positive and negative children had a similar number of vaccinations, and no vaccine was associated with the development of islet antibodies. Although other studies had found a protective effect from the BCG and MMR vaccines, the BABYDIAB data did not find any vaccine to have a protective effect on the development of autoantibodies.

The data from DAISY also failed to find any association between early immunizations and β islet cell autoimmunity. The Graves study[110] looked at the timing of the hepatitis B and Hib vaccines, the number of doses administered, and the median age at the first dose. This study found no differences between case and control children in the proportion who received hepatitis B vaccine at birth, before nine months of age, or in the median age at receipt of the first dose. Tr. at 286-90A. There were no statistically significant differences between the two groups in the mean number of doses administered and the mean age at first vaccination. Similar results obtained for the other vaccinations studied, which included polio, DTaP, and Hib. Tr. at 287-88.

Two Italian studies looked specifically for any association between the hepatitis B vaccination and either autoantibodies or T1D. The one published study[111] examined a number of autoantibodies, including those for diabetes, in 210 six-year-old children who were vaccinated at birth for hepatitis B, and in 109 unvaccinated children. No diabetes

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[107] With the possible exception of Dr. Classen's work, all of the recent studies that have looked for an effect of vaccinations on the development of either autoantibodies or T1D have failed to detect any association.

[108] 2002 IOM Report, Res. Ex. L, at 8. As the abstract indicates, this review examined potential biological mechanisms and epidemiologic evidence relating to vaccine causation of T1D. *Id.* at 1.

[109] M. Hummel, *et al.*, *No Major Association of Breast-Feeding, Vaccinations, and Childhood Viral Diseases With Early Islet Autoimmunity in the German BABYDIAB Study*, DIAB. CARE 23(7): 969-74 (2000), filed as Res. Ex. CCC, Tab 25.

[110] Res. Ex. CCC, Tab 99. Doctor Rewers was the senior researcher on this study.

[111] C. Belloni, *et al.*, *No evidence of Autoimmunity in 6-Year-Old Children Immunized at Birth with Recombinant Hepatitis B Vaccine*, PEDIATRICS 110(1): 1-4 (2002), filed as Res. Ex. CCC, Tab 100.

autoantibodies were detected in any of the children studied. One weakness of this study is that the children studied were not screened for genetic susceptibility to diabetes.

The second Italian study was not intentionally filed. It appeared in abstract[112] form on the same page of Res. Ex. CCC, Tab 9, as the Schatz PANDA abstract[113] that Dr. Rewers was citing. Two of the co-authors on the Italian study were Dr. John Classen and Mr. David Classen, and Doctor Rewers' cross-examination on this abstract brought both their professional reputations and the reported data into issue. The abstract reported an increased risk of T1D in children in Italy who received hepatitis B vaccines between two and three months of age and in those who were vaccinated at age 12.

Although he had not previously read the abstract of this particular study, Dr. Rewers described Dr. Classen as "pretty much discredited in terms of the research community by having significant conflict in those studies." Tr. at 302A. Doctor Rewers noted that this abstract appeared to be a meeting abstract, and that, as it was not followed by a published article, the scientific community would accord it little weight. According to Dr. Rewers, Dr. Classen had a penchant for reanalyzing data from studies to come to conclusions that the study's authors believed was not supported by their research. Tr. at 302A-04A. Doctor Rewers characterized Dr. Classen's work as "a pattern of creative data analysis...". Tr. at 304A. Based on the nature of the evidence

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[112] This abstract (P. Pozzilli, *et al.*, *Hepatitis B Vaccine Associated with an Increased Risk of Type 1 Diabetes in Italy*, ABSTRACTS FROM THE AMERICAN DIABETES ASSOCIATION 60TH SCIENTIFIC SESSION, 272-OR, A67) appears, with three other abstracts on the same page, on Res. Ex. CCC, Tab 9. According to Dr. Whitton, there are two forms of abstracts. Tr. at 429A-30A. A "meeting abstract" is an early draft of a study's conclusions, which may change in the final manuscript, particularly after peer review. A meeting abstract is not considered a published or peer reviewed paper. Tr. at 325-26. Meeting abstracts are, by their nature, preliminary and curtailed reports of research. The failure to publish a paper based on an abstract is a strong indicator that the initial report was incorrect or inadequately supported by later findings. Tr. at 303-04A. In contrast, the summary of a paper's findings and conclusions contained within a paper is also called an abstract. This type of abstract is searchable on PubMed (a research database), and if the paper has been peer reviewed, the abstract is generally credible. Tr. at 429A-30A. Peer review helps distinguish between possibilities and probabilities. Tr. at 325-26. Doctor Whitton called peer review "the cornerstone of science." Tr. at 344. When medical literature is submitted as evidence, the type of medical literature submitted may be weighed and evaluated in determining what weight should be accorded to that evidence. The Supreme Court has noted:

> [S]ubmission to the scrutiny of the scientific community is a component of "good science," in part because it increases the likelihood that substantive flaws in methodology will be detected. The fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is premised.

Daubert, 509 U.S. at 593-94 (citations omitted).

[113] D. Shatz, *et al.*, *Prospective Assessment in Newborns for Diabetes Autoimmunity (PANDA): A Newborn Diabetes Screening Program in the State of Florida*, DIAB. 49(1): A67 (2000), filed as Res. Ex. CCC, Tab 9.

described in the abstract, Dr. Rewers testified that no causal relationship could be established between the vaccine and T1D. He noted that the abstract did not include the actual numbers of case children or controls. Tr. at 306-07A, 309-10A. Doctor Whitton echoed his concern about the missing numbers, commenting that numbers are important in assessing the weight to be given a conclusion. Tr. at 453B.

Although petitioner relied on this abstract (*see* Pet. Post-Hearing Br. at 46-47), noting the similarity of Mr. Hennessey's age at vaccination to the age of the children in one of the groups in which a connection was drawn between the hepatitis B vaccine and T1D onset, the abstract apparently never resulted in a published paper. I note that Dr. Rewers suggested that petitioner's counsel contact one of the primary researchers to ascertain why the abstract never resulted in a published paper. Tr. at 309-10A. No further evidence regarding this study was introduced, and therefore, I have accorded the abstract very little weight.[114]

A U.S. case-control study[115] examined the possible connection of hepatitis B vaccination (in both infants and older children) with T1D diagnoses (as compared to the development of autoantibodies). The DeStefano study compared 252 children with diagnosed T1D to 768 controls, looking at hepatitis B, pertussis, MMR, Hib, and varicella vaccinations. There was no increased risk of T1D for any of the vaccines studied. Additionally, the authors conducted a separate analysis of the hepatitis B vaccine for those who received the initial dose at birth versus those who received it later in life.[116] Because the study considered children born between 1988 and 1997, the oldest study participants were close to Mr. Hennessey's age. The controls were closely matched to the case children, based on enrollment in the same health maintenance organization, length of enrollment in that HMO, age, and gender. Using logistic regression analysis of the data, to include the additional variables of race, ethnicity, and family history of T1D, there was no association found between administration of hepatitis B (or any other vaccine) and development of T1D. Forty-four percent of the case children (those with T1D) received the hepatitis B vaccine. The odds ratio developed was 0.73. Standing alone, this odds ratio would indicate a protective effect of the vaccine, because the odds

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[114] I have attached little weight to the Schatz abstract, also appearing on Res. Ex. CCC, Tab 9, for the same reason. Likewise, although Dr. Rewers testified about unpublished data from his research that he had recently presented at the International Diabetes Society Congress (Tr. at 265-67), I have attached little weight to his testimony about that research data. I emphasize that I am not establishing a *per se* rule against considering studies, reports, or articles that are not peer reviewed, only that in this case, with the wealth of peer reviewed data available for consideration, the lack of peer review adversely affects the weight I attach to conclusions drawn in these exhibits and testimony. *See Daubert*, 505 U.S. at 593-94.

[115] DeStefano, Res. Ex. CCC, Tab 92.

[116] This was another of the many studies that tested (and refuted) the Classen hypotheses that timing of certain vaccinations, including hepatitis B, may affect the risk of developing T1D and that the Hib vaccine may be associated with T1D. DeStefano, Res. Ex. CCC, Tab 92, at 2 (using the machine generated page numbers in the lower right hand corner of each page).

ratio was less than one.[117] However, the confidence interval of the study was 0.45-1.19, indicating that, based on a single study, the determination of a protective effect would be unreliable. As Dr. Rewers explained, the only scientifically sound conclusion is that there was no association between the vaccine and T1D. Tr. at 292-95A; Res. Tr. Ex. 2, p. 21.

The DeStefano study also examined the timing of hepatitis B vaccinations. Regardless of the age of the child at the time of the first dose of hepatitis B vaccination, children who received the vaccination had lower odds of developing T1D than those who did not receive hepatitis B vaccinations, but the differences were not statistically significant. Tr. at 296A-97A; Res. Tr. Ex. 2, p. 22. Doctor Rewers' group performed a similar study in 2001, but used two control groups.[118] Tr. at 297A; Res. Tr. Ex. 2, pp. 26-28. The filed abstract reported results similar to those in the DeStefano study. However, because I cannot determine from the abstract if this was a peer reviewed study, I have elected to place no weight upon it.

A very large Finnish study[119] looked at the Hib vaccine and the incidence of T1D in 246,000 children, comparing those who received one dose of Hib vaccine at 24 months of age to those who received three or four doses beginning at two months of age. There was no difference in the incidence of T1D diagnoses between the two groups. Tr. at 290. Because the dosing schedules were so different, if timing of vaccination or the number of doses played any role in the development of T1D, a difference in the incidence of T1D between the two groups would have been observed.

Because the Danish national registry tracks both cases of T1D and all vaccinations, Danish studies have the twin advantages of large numbers and easy access to medical data. The Hviid study[120] evaluated a cohort consisting of all children born during a 10 year period in Denmark, with detailed information on vaccinations (Hib, diphtheria, tetanus, polio, acellular pertussis, whole cell pertussis, and MMR) and T1D diagnoses available. No association of any vaccine with T1D was found. The study also separately evaluated vaccinations in genetically predisposed children (those with a sibling with T1D), and found no significant association with T1D. There was no evidence that cases of T1D clustered in the two to four years after vaccine administration. Tr. at 291A-92.

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[117] However, if several studies all demonstrate an odds ratio in the vicinity of 0.7, then a meta-analysis of all the data might demonstrate a protective effect of a vaccine. Tr. 294A-95A.

[118] P. Carossone-Link, *et al.*, *Childhood Vaccinations and Type 1 Diabetes*, DIAB. 50(Suppl 2): A209 (2001), filed as Res. Ex. CCC, Tab 90.

[119] M. Karvonen, *et al.*, *Association between type 1 diabetes and Haemophilus influenzae type b vaccination: birth cohort study*, BMJ 318: 1169-72 (1999), filed as Res. Ex. CCC, Tab 89.

[120] Hviid, Res. Ex. CCC, Tab 91. This was yet another study testing, and refuting, the Classen hypotheses regarding vaccination and T1D. *Id*. at 1403.

The Hviid study was previously cited by Dr. Shoenfeld as "well-conducted" and demonstrating no causal relationship between vaccines and T1D. Tr. at 93A, 98A-99; Pet. Ex. 38 at 313. However, he testified at the hearing that, based on his acquisition of information on the protective effect of vitamin D, he could no longer rely on this study because vitamin D intake was a possible confounder. He indicated that the authors would have been unaware of the protective effects of vitamin D at the time of their study. Tr. at 98A. Given that the Hviid study was published in 2004, based on children in Denmark, and the studies showing a protective effect of vitamin D were published in 1999 (Finland), 2001 (Sweden) and 2003 (Norway), Dr. Shoenfeld's speculation is not likely accurate.

(3) Evidence Regarding Thimerosal and Adjuvants.

The epidemiologic evidence strongly suggests that the hepatitis B vaccine is not likely to be causal of T1D or the initiation of the β islet cell destruction that precedes insulin dependence. Thus, it is unlikely that either the aluminum salt adjuvant or the thimerosal preservative contained in the hepatitis B vaccine are causal. Although Dr. Shoenfeld testified about several potentially causal mechanisms by which mercury or aluminum could trigger an autoimmune process,[121] neither his testimony nor his report pointed to any evidence indicating that the theoretical mechanism worked in practice. At best, he pointed to an article dealing with the immune system effects of arsenic. Tr. at 38A-41A.

The lack of evidentiary support for Dr. Shoenfeld's theories regarding the possible roles of thimerosal (ethylmercury) and aluminum adjuvant in initiating either autoantibodies to β islet cells or the development of insulin dependence is illustrated by Dr. Bercu's report. He noted that "there are no studies (published or planned) specifically addressing ethylmercury as a cause of diabetes." Res. Ex. A at 2. However, he cited several studies addressing the role of methlymercury in diabetes.

A 1976 study[122] determined that methylmercury chloride could disturb the pancreatic β islet cells of rats, resulting in high blood glucose. The hypothesis that mercury exposure in humans could contribute to diabetes was based, in part, on evidence from the Minamata Bay methylmercury disaster in Japan, showing pancreatic islet injury in some individuals exposed. The Shigenaga study attempted to develop an animal model of this injury for further study. However, an epidemiologic study

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[121] These included modulating the toll-like receptors on host cell surfaces to make them recognizable to the host's own immune system (Tr. at 35, 39A, 68), modulating the proteins contained in the vaccine to make them more immunogenic (Tr. at 49), modulating the pancreatic antigens (Tr. at 68), or enhancing an already ongoing autoimmune reaction (Tr. at 47).

[122] K. Shigenaga, *Pancreatic Islet Injury Induced by Methyl Mercuric Chloride Light and Electron Microscopic Studies*, KUMAMOTO MED. J. 29(2): 67-81 (1976) ["Shigenaga"], filed as Res. Ex. D.

(Futatsuka 1996)[123] of the Minamata victims failed to find any increased prevalence of diabetes in the mercury-exposed population. Four years later, a followup case-control study[124] found no increased prevalence of diabetes mellitus from the participants in the Futatsuka 1996 study. Futatsuka 2000, Res. Ex. F at 89.

As the reported studies of diabetes and mercury involved methyl, not ethylmercury, they are not particularly informative of the role, if any, that ethylmercury might play. Similar chemical compounds may behave differently in the human body, as illustrated by the difference in effects from methyl and ethyl alcohol. *See Snyder*, 2009 WL 332044 at * 63 (discussing the different forms of mercury and alcohol). However, as petitioner did not file any evidentiary support for Dr. Shoenfeld's assertions concerning thimerosal's or ethylmercury's possible influence on the development of autoimmunity, these three studies constitute the only evidence about a possible role for mercury. I note that none of Dr. Shoenfeld's references discussed the role of mercury in instigating autoimmunity and had only passing references to adjuvants. In a lengthy discussion by Dr. Shoenfeld and a co-author of possible environmental triggers of autoimmunity, neither mercury nor aluminum were mentioned. *See* V. Molina and Y. Shoenfeld, *Infection, vaccines and other triggers of autoimmunity*, AUTOIMMUNITY 38(3): 235-45 (2005) ["Molina and Shoenfeld"], filed as Pet. Ex. 37.

The only reference to discuss other chemicals as environmental toxins with regard to T1D was a literature survey[125] of possible environmental factors associated with an increased risk of T1D. The only two chemicals identified were arsenic and dioxin, neither of which was identified as a vaccine component.

In contrast to Dr. Shoenfeld's testimony, Dr. Whitton testified that there was no evidence to show that the very small amounts of ethylmercury in the thimerosal preservative in vaccines were harmful. Tr. at 350. Doctor Whitton also testified that he had found no evidence to suggest that the aluminum salt adjuvant in some vaccines, including hepatitis B, was harmful, much less that it could cause T1D. Tr. at 353A-54. Also in contrast, Dr. Bercu, whose report and accompanying articles evinced a thorough grounding in diabetes research, indicated that thimerosal was not being considered as a diabetogenic toxin. Res. Ex. A at 1, 4. He noted the publicity that accompanied thimerosal's removal from most vaccines and commented: "[I]t is inconceivable to me

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[123] M. Futatsuka, *et al.*, *An Epidemiological Study on Diabetes Mellitus in the Population Living in a Methyl Mercury Polluted Area*, J. EPIDEM. 6(4): 204-08(1996) ["Futasuka 1996"], filed as Res. Ex. E.

[124] M. Futatsuka, *et al.*, *Health Surveillance in the Population Living in a Methyl Mercury-Polluted Area over a Long Period*, ENVTL. RES. SEC. A 83: 83-92 (2000) ["Futasuka 2000"], filed as Res. Ex. F. The introduction to this article and a portion of the discussion section describes the Minamata mercury disaster and the extensive studies of various medical problems of the survivors.

[125] V. Parker, *et al.*, *Toxins and Diabetes Mellitus: An Environmental Connection?* DIAB. SPECTRUM 15(2): 109-12 (2002), filed as Res. Ex. G.

that researchers would ignore thimerosal as a potential factor if there were any indication that it might contribute to type 1 diabetes. The fact that thimerosal is not a research subject shows that scientists do not think it is even remotely plausible that thimerosal causes beta cell destruction and diabetes mellitus." *Id*. at 4. *See also* Res. Ex. C, NIH T1D Strategic Plan, at 17 (describing TEDDY's goal as identifying environmental causes of T1D in genetically susceptible individuals).

b. Other Evidence that Vaccinations are Unlikely as Causal Factors.

In addition to the studies that found no association between vaccines in general, and the hepatitis B vaccine in particular, with the development of T1D or autoantibodies, other evidence suggests that the hepatitis B vaccine was unlikely to be causal of T1D generally and in Mr. Hennessey's specific case.

The incidence of T1D in children from birth to age 14 has been rising for at least 50-60 years. Finland has the best registry of the disease, going back to about 1950. As other countries noticed similar increases in the incidence of the disease, they began diabetes registries as well. Information from Pittsburgh beginning in 1965 shows the same pattern in the U.S. as in Finland. The chart at Res. Trial Ex. 2 at 1 reflected relatively parallel incidence rates over time for Finland, Sweden, Colorado, and Germany, with rates rising at a level of about three to five percent per year. Tr. at 259-60.

The hepatitis B vaccine was available in all the countries on the chart, beginning in 1988-89. However, there was no sudden spike in incidence rates (over the 3-5% annual rise) after the introduction of the vaccine. Immediately after the vaccine was introduced, it was given to many children as catch-up doses, so many more doses were administered in the first two years after the vaccine became available than in subsequent years. The number of catch-up vaccinations is now very low, as most babies receive their three hepatitis B vaccinations during the first six months of life. There has been no decline in the incidence rate of T1D as the number of catch up doses administered has declined. Tr. at 259-60; Res. Tr. Ex. 2, p. 1.

With the exception of Dr. Classen's questionable publications, there is no epidemiologic evidence of an association between any vaccine and T1D. There are, however, numerous, highly consistent studies refuting such an association. When the hepatitis B vaccine data is separately analyzed, there is, likewise, no evidence of any association between this vaccine and clinically overt T1D or the appearance of autoantibodies. Taken as a whole, the scientific evidence indicates that vaccines do not initiate this autoimmune process, nor do they accelerate it into clinically overt T1D. As Dr. Maclaren testified, with regard to vaccine causation of T1D: "There just isn't any smoke, let alone a fire that we can see in this." Tr. at 178-79.

(1) The Diseases Against Which Vaccines are Administered Do Not Appear to Play a Causal Role in T1D.

Although some evidence suggests that viruses, particularly enteroviruses, may have some role in accelerating the development of insulin dependence, if not in the initiation of autoantibodies, there is no evidence that any of the diseases against which children are routinely vaccinated are causal, with the exception of congenitally acquired rubella.

The evidence for any other viruses causing T1D consists only of case reports. Although case reports may be filed as evidence in Vaccine Act cases, the *Reference Manual on Scientific Evidence*, FEDERAL JUDICIAL CENTER, 2000 (2d ed.), notes that, in determining medical causation: "[c]ausal attribution based on case studies must be regarded with caution," largely because they lack controls and, thus, do not provide the level of information or detail found in epidemiologic studies. *Id*. at 475. A temporal association, standing alone, is insufficient as evidence of causation. Petitioners have the burden to demonstrate the existence of a "scientific temporal relationship." *Pafford v. HHS*, 64 Fed. Cl. 19, 29-30 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). The time frame must be "medically acceptable." *De Bazan*, 539 F.3d at 1352. In the case of a disease with a long latency period between the first appearance of autoantibodies and clinically overt disease, such as T1D, a close temporal relationship between virus (or vaccine) and symptoms of T1D is virtually meaningless with regard to cause and effect, because the virus or vaccine was likely encountered at a time when the β islet cell destruction was already far advanced.

With regard to the virus alleged to be causal in Mr. Hennessey's case, there are not even case reports suggesting an association between hepatitis B virus and clinically evident T1D. If the hepatitis B virus could cause T1D, high rates of T1D should be seen in those countries where hepatitis B infections are high. There would also be differences in rates of T1D before and after the vaccine was introduced. However, no such differences have been noted. Tr. at 179-80. Doctor Shoenfeld attempted to explain away the lack of any case reports by saying that hepatitis B is rare in children, in whom T1D is most frequently diagnosed and, thus, there are not enough cases to demonstrate a connection. Tr. at 63. Doctor Whitton disagreed, noting the epidemic nature of hepatitis B infections, particularly in the Far East, prior to the introduction of the vaccine, and testifying that millions of children acquired the virus congenitally. Tr. at 360B-62B. The lack of any reported association between hepatitis B and T1D suggests that even if the hepatitis B surface antigen can stimulate an autoimmune reaction, it does not do so in pancreatic β cells. Therefore, a vaccine containing that surface antigen is unlikely to do so, either. Tr. at 362B-63B.

(2) Vaccines as Triggers of Accelerated β Islet Cell Destruction.

Doctor Shoenfeld testified that a person who had new onset of T1D might still be harmed by a vaccine, because a vaccine could affect the honeymoon period, during

which the body continues to produce some insulin. Tr. at 90-92. Doctor Rewers disagreed, stating that there was no mechanism by which a hepatitis B vaccination could have accelerated the process of β islet cell destruction in Mr. Hennessey. In infectious diseases that cause a fever, blood glucose levels in those with T1D increase, thus increasing the need for insulin. However, based on his experience, patients with T1D who receive vaccinations, such as hepatitis B vaccinations, do not experience a similar rise in blood glucose levels, indicating no effect on insulin. Therefore, it appears unlikely that the hepatitis B vaccination accelerates the process of β islet cell destruction, leading to a rise in blood glucose. Tr. at 234-35.

In Mr. Hennessey's case, there is good evidence to indicate that the hepatitis B vaccines did not adversely affect the insulin production capacity remaining after his diagnosis. Mr. Hennessey had two hepatitis B vaccines prior to his diagnosis with T1D, and one approximately 50 days after his diagnosis, in January, 1999. This third hepatitis B vaccine occurred when Mr. Hennessey was still in his diabetic honeymoon period. *See* Pet. Ex. 5, pp. 9, 12, and 13 (references by Dr. Kyllo to Mr. Hennessey still being in the honeymoon period in March, 1999, over two months after his third hepatitis B vaccination). Not only did the vaccine have no apparent ill effect on his blood glucose levels, during the three months after his third vaccine, his HB A_{Ic} levels continued their decline to a low of 6.9%.[126] If, as Dr. Shoenfeld hypothesized, the two earlier hepatitis B vaccines triggered an acceleration of his β islet cell destruction, why was there no similar effect from the third vaccination? The honeymoon effect indicates that Mr. Hennessey continued to produce insulin after the third hepatitis B vaccination in sufficient amounts to support his insulin therapy in controlling his blood glucose.

3. Evidence Regarding Causation of Celiac Disease.

Because Dr. Shoenfeld's testimony, which was the only evidence causally connecting Mr. Hennessey's T1D to his celiac disease, did not reach the preponderance standard, it may be unnecessary to address the evidence rebutting the suggestion that there was a causal connection.[127] However, because the Federal Circuit decisions regarding the preponderance standard appear to conflict (compare *Knudsen* cite to *Pafford* cite), I address the reasons I found Dr. Shoenfeld's testimony on causation unpersuasive and insufficient.

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[126] Six months after the third hepatitis B vaccine, Mr. Hennessey's HB A_{Ic} level was only slightly higher at 7.6%, at a time when Dr. Kyllo still considered Mr. Hennessey to be in the honeymoon period. Pet. Ex. 5, p. 16.

[127] To review Dr. Shoenfeld's testimony, he stated that people with one autoimmune disease are predisposed to get a second autoimmune disease. Thereafter, he testified, "it might be that the celiac disease was also the direct consequence of the vaccine. It might be not. We will never know it, and we cannot say under oath to the right way or to the left way." Tr. at 71.

Doctor Shoenfeld's testimony and report suggested that there was a causal connection between T1D and celiac disease, rather than merely a common genetic susceptibility. Other than his theory that all autoimmune diseases are the same disease, he offered no support for this opinion. The evidence adduced (and some of his own testimony)[128] contradicted his opinion. The clear weight of scientific opinion is that celiac disease is caused by the exposure of a genetically susceptible individual to gliadin, and that there exists no cause and effect relationship with T1D. Celiac disease and T1D do not have a causal relationship with one another, merely a common genetic susceptibility. Tr. at 234, 348. *See also* Eisenbarth, Res. Ex. Q, at 401. Thus, assuming, *arguendo*, that Mr. Hennessey's T1D was vaccine-induced, there is no evidence that his T1D made him more or less susceptible to celiac disease.

In later testimony, Dr. Shoenfeld appeared to acknowledge that environmental factors trigger celiac disease. Tr. at 118. Although some of the disagreement between Dr. Shoenfeld and respondent's experts appeared to be caused by what is meant by "having" celiac disease, the difference was more fundamental. Doctor Shoenfeld testified that by avoiding some substances, a person with celiac disease would not be symptomatic. *Id*. His testimony indicated that, before onset of the T1D, Mr. Hennessey may have been in the preclinical stage of celiac disease, but because no one tested him for antigliadin antibodies, it was impossible to know. Tr. at 119.

However, Drs. Maclaren, Rewers, and Whitton all testified that Dr. Shoenfeld was simply incorrect when he called celiac disease "a known complication" of T1D. Tr. at 137, 234, 447A-48A. *See also* Res. Exs. RR at 6, X at 1, and AAA at 9-10. Celiac disease is an autoimmune disease with a known trigger or cause: exposure to gliadin. Tr. at 170B. Doctor Maclaren characterized it as a "companion disorder, not caused from diabetes, but an associated disorder...". Tr. at 137. Doctor Rewers indicated that his research facility had tested nearly 2,400 children for celiac antibodies. In the majority of those tested, the antibodies appeared at around two years of age. Tr. at 271A.

The weight of the evidence is that there is no cause and effect relationship between celiac disease and T1D, and that vaccines do not play any role in the development of celiac disease. Tr. at 173. *See also* M. Rewers, *et al.*, *Celiac disease associated with type 1 diabetes mellitus*, ENDOCRINOL. METAB. CLIN. N. AM. 33: 197-214 (2004), filed as Res. Ex. CCC, Tab 101 (a summary of the spectrum of celiac disease, current and recommended screening, and genetic susceptibility factors). This article mentions (but does not adopt) the opinion of some researchers that celiac disease may predispose one to T1D, not the converse.

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[128] In testifying that all autoimmune diseases are the same disease, Dr. Shoenfeld acknowledged that the type of genetic predisposition varies from one autoimmune condition to another, and that the immune defects caused by the genetic background vary from disease to disease. Tr. at 18-20. This does not sound like a description of "the same disease."

IV. Law Applicable to Off-Table Causation Claims.

A. Proving Causation.

To demonstrate legal cause in off-Table injury claims, Vaccine Act petitioners must establish each of the three *Althen* factors: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. 418 F.3d at 1278. Circumstantial evidence and medical opinions may be sufficient to satisfy the second *Althen* factor. *Capizzano*, 440 F.3d at 1325-26.

The medical theory factor does not require petitioners to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of an injury or condition; showing that the vaccination was a "substantial factor" in causing the condition and was a "but for" cause are sufficient for recovery. *Shyface,*165 F.3d at 1352. *See also Pafford v. Sec'y, HHS,* 451 F.3d 1352, 1355 (Fed. Cir. 2006) (petitioner must establish that vaccinations were a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners may not be required to show "epidemiologic studies, rechallenge, the presence of pathologic markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect...". *Capizzano*, 440 F.3d at 1325. Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen v. Sec'y*, *HHS* 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280. *But see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof failed to meet that burden).

When a petitioner alleges an "off-Table" injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioner demonstrates that he: (1) received, while within the United States, a vaccine listed on the Vaccine Injury Table; (2) sustained an illness, disease, disability, or condition caused by the vaccine (or experienced a significant aggravation of an illness); and (3) experienced the effects of the vaccine injury for more than six months.[129] Vaccine litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or whether the symptoms have persisted for the requisite time. In this case, the focus, as in most

[129] Section 300aa–13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1)...". Section 300aa–11(c)(1) contains the factors listed above, along with others not relevant to this case, including exceptions to the "within the U.S." factor.

vaccine litigation, is on the issue of whether the injury alleged was caused by the vaccine; all of the other requirements of the Vaccine Act were established.

In an off-Table case, if the special master concludes that petitioner's evidence of causation is lacking, then the burden never shifts to respondent to demonstrate the "factors unrelated" as an alternative cause for petitioner's injury. *See Bradley,* 991 F.2d at 1575 (when petitioner has failed to demonstrate causation by a preponderance, alternative theories of causation need not be addressed) and *Johnson v. Sec'y, HHS*, 33 Fed. Cl. 712, 721-22 (1995), *aff'd*, 99 F.3d 1160 (Fed. Cir. 1996) (even in idiopathic disease claims, the special master may conclude petitioner has failed to establish a *prima facie* case). In *De Bazan*, 539 F.3d at 1353-54, the Federal Circuit explicitly stated that the special master may consider all of the evidence presented, including that of respondent, in determining whether petitioners have met their burden of proof.

B. Proving Significant Aggravation.

Petitioner presented a significant aggravation claim, rather than one of causation itself. His reliance on a significant aggravation theory was dictated by the substantial body of evidence indicating that insulin dependence is preceded by years of slow β islet cell destruction.

To some degree, the nature of petitioner's theory is immaterial. Because this is an off-Table case, the Federal Circuit's four part test, set forth in *Whitecotton v. Sec'y, HHS*, 81 F.3d 1099 (Fed. Cir. 1996) ["Whitecotton II"] is not applicable.[130] Whether he presents a direct causation case or a significant aggravation case, the petitioner in an off-Table case must still prove that the vaccine played a causal role in the aggravation of the underlying condition. Unlike the situation presented in *Whitecotton II,* where causation was presumed because of the Table injury claim,[131] a petitioner in an off-Table significant aggravation claim cannot merely demonstrate a significant worsening of a preexisting condition; he must also show that the vaccine was a legal cause of that significant worsening.

To illustrate, if someone with preexisting idiopathic brachial neuritis received a tetanus vaccine and thereafter experienced a worsening of that condition (such as by

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[130] The *Whitecotton II* four part test involves: (1) assessing the vaccinee's condition prior to administration of the vaccine; (2) assessing the vaccinee's current condition; (3) determining if the current condition constitutes a significant aggravation of the preexisting condition; and (4) determining if the alleged vaccine-aggravated Table injury occurred within the Table time frame. 81 F.3d at 1107. Of course, the unstated threshold question, which must be answered before the *Whitecotton II* test is applied, is whether the condition aggravated is a Table injury.

[131] In a Table injury claim, causation is presumed when a listed injury occurs within the Table's specified time frame. When a vaccine is alleged to have aggravated a preexisting Table condition, the focus is on determining to what extent, if any, the vaccine aggravated the condition, not on causation.

increased pain and muscle atrophy), the logical place to begin the analysis is with *Whitecotton II's* fourth factor--whether this Table injury's symptoms occurred within the time frame specified on the Table. If so, then the focus of the entitlement inquiry would shift to a comparison of petitioner's condition before and after the tetanus vaccine (the first two *Whitecotton II* factors), followed by a determination of whether the injury constituted, per the statute, "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by a substantial deterioration of health." § 300aa-33(4). The special master would not be required to address the *Althen* factors to determine whether the tetanus vaccine caused the aggravation of the condition; such aggravation would be presumed. Of course, respondent would be free to demonstrate that the change in the petitioner's condition was caused by something other than the vaccine–the "factors unrelated" from § 300aa-13(a)(1)(B)–by a preponderance of the evidence.

When a vaccination is alleged to be the cause of a significant aggravation of a preexisting, off-Table injury, petitioner retains the burden of showing legal cause. That is, petitioner must demonstrate by preponderant evidence that the vaccine was a "substantial factor" in, and a "but for" cause of, his current condition by adducing evidence supporting each of *Althen's* three factors.

In the off-Table significant aggravation claim, it is not entirely clear to what extent the *Whitecotton II* factors apply. In a recent decision by the Court of Federal Claims, *Loving v. Sec'y, HHS*, 86 Fed. Cl. 135 (2009), Judge Lettow proposed a six factor test, requiring a petitioner to establish by preponderant evidence: (1) the vaccinee's condition prior to administration of the vaccine; (2) the vaccinee's current condition or condition following the vaccine; (3) whether the comparison of the two conditions constitutes a significant aggravation of the person's condition; (4) a medical theory causally connecting a significantly worsened condition to the vaccine; (5) a logical sequence of cause and effect demonstrating that the vaccine was the reason for the significant aggravation; and (6) a proximate temporal relationship between the vaccine and the significant aggravation. *Loving*, 86 Fed. Cl. at 144. The *Loving* test involves a melding of the first three *Whitecotton II* factors with a subtle reformulation of *Althen's* three factors, focusing the *Althen* inquiry on the significant aggravation of a preexisting condition, rather than on the cause of that condition.

The *Loving* test differs from a test previously formulated by the then-Claims Court, in *Misasi v. Sec'y, HHS*, 23 Cl. Ct. 322 (1991). The *Misasi* test required the trier of fact to "(1) assess the individual's condition prior to the administration of the vaccine, i.e., evaluate the nature and extent of the individual's preexisting condition, (2) assess the individual's current condition after the administration of the vaccine, (3) predict the individual's condition had the vaccine not been administered, and (4) compare the individual's current condition with the predicted condition had the vaccine not been administered." 23 Cl. Ct. at 324. Judge Andewelt concluded that the special master's analysis had addressed all four factors, because his causation determination was based

on "a thorough review and analysis of the injured person's condition before and after the vaccination in question, including consideration of what changes could reasonably have been expected in the course of the condition in the absence of aggravation." 23 Cl. Ct. at 325, n.1 (quoting the special master's slip opinion at 5).

The *Misasi* test was slightly altered by another decision of the Claims Court, *O'Connor v. Sec'y, HHS*, 24 Cl. Ct. 428 (1991), *aff'd* 975 F.2d 868 (Fed. Cir. 1992). In *O'Connor*, the court noted that the *Misasi* test "should not be construed as altering the petitioners' initial burden when demonstrating presumed causation [*i.e.*, in Table cases] under § 300aa-13(a)(1)(A)." 24 Cl. Ct. at 430, n.2. The court further held that respondent had the burden to show an alternate cause, which, in significant aggravation cases, could be met by demonstrating that the natural progression of the preexisting condition accounted for the vaccinee's current condition. 24 Cl. Ct. at 430, n.2. *See also Reusser v. Sec'y, HHS*, 28 Fed. Cl. 516, 526-28 (1993) (evaluating a claim that the special master erred in placing the burden on petitioners to establish prongs three and four of the *Misasi* test, and concluding that the *Misasi* test was inappropriate in the context of a Table claim, unless respondent first established the preexisting condition as causal). Whether this alteration was necessary in off-Table significant aggravation cases was not addressed, because neither *O'Connor* nor *Reusser* were off-Table cases.

Although the Federal Circuit's opinion in *Whitecotton II* also expressed concern that the *Misasi* test involved an improper shift of the evidentiary burden to petitioner, it expressed that concern in the context of a Table injury claim. When the injury alleged to be significantly aggravated is an off-Table condition, establishing that the vaccine was a significant factor and a but for cause of the significant aggravation is a burden that rests with petitioner. Thus, it is not enough for Mr. Hennessey merely to show that he was worse after the administration of the vaccines. To show legal cause, Mr. Hennessey must demonstrate that the hepatitis B vaccines were a significant factor in moving him from autoantibody positive to insulin dependence and that, but for the administration of these vaccines, he would not have developed insulin dependence when he did, if at all.[132]

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[132] A complicating factor in this analysis is that some individuals who are positive for one autoantibody may never develop T1D, although someone who is positive for two or more autoantibodies is approximately 90% likely to go on to develop insulin dependence. Tr. at 238-39. Also, someone who is persistently autoantibody positive may not develop insulin dependence for many years after the first autoantibody's appearance. The testimony indicated that T1D is sometimes diagnosed in octogenarians after decades of positive autoantibodies. Placing the burden on a petitioner to demonstrate that he would never have moved from the autoantibody positive phase to insulin dependence, but for the vaccine, may be too heavy a burden. However, assuming, *arguendo*, that a vaccine can accelerate the onset of T1D, another issue is raised. That is: how much of an acceleration is needed to constitute a significant aggravation? If someone develops insulin dependence two years earlier than he might otherwise have done, the time frame may constitute significant aggravation. Two additional years of insulin shots, coupled with an increased risk of diabetes complications during those two years, may well constitute a significant aggravation. On the other hand, a two-day acceleration in onset of insulin dependence may not be a significant aggravation. This issue is somewhat akin to the "loss of chance" cases that are permitted in

In *Whitecotton II*, the Federal Circuit called significant aggravation the "most slippery and difficult to apply" concept embodied in the Vaccine Act. 81 F.3d at 1105. Applying the *Misasi*, *O'Connor*, or *Loving* tests in the context of an off-Table injury of this nature is likewise difficult. Determining where to begin the analysis is complicated by the nature of Mr. Hennessey's preexisting condition and the need to consider what it means to "have" T1D. I address this issue in the context of evaluating Mr. Hennessey's condition before and after the vaccines.

In most off-Table significant aggravation cases, it may be more logical to consider the last three *Loving* factors first. That is, if the evidence does not establish vaccine causation of the vaccinee's current condition, it does not matter whether he is worse after the vaccine than he was before the vaccine, because he has failed to show that the vaccine was responsible for any worsening of his condition. However, in the case of a condition like T1D, in which the demarcation between the stages of the condition may be subtle or silent (not clinically overt), and in which some individuals may never progress beyond the appearance of one autoantibody, a critical examination of Mr. Hennessey's condition before and after the vaccines is essential in determining whether the change for the worse in his clinical presentation was aggravation or a natural progression of the underlying β islet cell destruction. To analogize, does one "have" lung cancer only when it is clinically overt and diagnosed?

C. Resolving Conflicting Evidence.

In Vaccine Act cases, special masters are frequently confronted by witnesses with diametrically opposed positions on causation. When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. Objective factors, including the qualifications, training, and experience of the expert witnesses and the extent to which their proffered opinions are supported by reliable medical research, other testimony, and the factual basis for their opinions, are all significant in determining what testimony to credit and what to reject. Witness demeanor is an important subjective factor.

If merely an opinion supporting vaccine causation, without more, were all that is necessary to meet petitioner's burden of proof, surely Congress would have said so. Congress could also have said that any injury temporally connected to a vaccine is compensable. It did not. Even in Table injury cases, where petitioners benefit from a presumption of causation, respondent may introduce evidencing negating vaccine

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some states in conventional tort litigation, where a negligent failure to diagnosis cancer at an early stage results in reduced chance of a cure or a reduction in the five year mean survival rate. *See, e.g.*, *Anderson v. Brigham Young University*, 89 F.3d 849 (10th Cir. 1996). *See generally*, Nancy Levit, Ethereal Torts, 61 GEO. WASH. L. REV. 136 (1992) (discussing "loss of chance" and other intangible tort causes of action). For purposes of analyzing Mr. Hennessey's significant aggravation claim, I will assume, without deciding, that any acceleration, however slight, in the time period before insulin dependence occurs constitutes a significant aggravation of the underlying condition of β cell destruction.

causation by presenting causal "factors unrelated" to the vaccine alleged.[133] By specifying petitioners' burden of proof in off-Table cases as the preponderance of the evidence, directing special masters to consider the evidence as a whole, and stating that special masters are not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in that record, Congress clearly contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof.[134] In weighing and evaluating expert opinions in Vaccine Act cases, a special master uses the factors governing admissibility that the Supreme Court considered important to provide the weights and counterweights in determining which opinions to accept. *See Kumho Tire Company, Ltd., v. Carmichael,* 526 U.S. 137, 48-50(1999) and *Terran*, 195 F.3d at 1316.

The special master determines the reliability and plausibility of the expert medical opinions offered and the credibility of the experts offering them. Not all evidence carries equal weight with a trier of fact.[135] A medical opinion on causation may be based on factually incorrect medical histories, or it may be offered by someone without the necessary training, education, or experience to offer a reliable opinion. An expert's opinion may be unpersuasive for a variety of reasons.[136] Courts, whether they deal with vaccine injuries, medical malpractice claims, toxic torts, or accident reconstruction, must

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[133] *See* § 300aa-13(a)(2).

[134] *See* §§ 300aa–13(a)(1)(A) (preponderance standard); § 13(a) ("Compensation shall be awarded...if the special master or court finds on the record as a whole..."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation); and § 13(b)(1) (special master not bound by any particular piece of evidence).

[135] I note that, in civil jury trials, the jurors are commonly instructed that they are not required to rely on the testimony of any particular expert witness. *See, e.g.*, 7th Circuit Pattern Jury Instruction 1.21 Expert Witnesses, www.ca7.uscourts.gov/7thcivinstruc2005.pdf (last visited May 8, 2009) ("The fact that [an expert witness] has given an opinion does not mean that you are required to accept it. Give the testimony whatever weight you think it deserves, considering the reasons given for the opinion, the witness's qualifications, and all of the other evidence in the case."). *See generally*, *United States v. Mansoori,* 304 F.3d 635, 654 (7th Cir. 2002), *cert. denied*, 538 U.S. 967 (2003). The Federal Circuit has described a special master's credibility determinations as "virtually unreviewable." *Bradley v. Sec'y, HHS,* 991 F.2d 1570, 1575 (Fed. Cir. 1993). *See also Energy Capital Corp. v. United States*, 302 F.3d 1314 (2002) ("As for the relative weight given to the testimony of both sides' expert witnesses, we accord the trial court broad discretion in determining credibility because the court saw the witnesses and heard their testimony.").

[136] Jurors in civil trials are commonly instructed that it is their duty to judge the credibility of witnesses. In making credibility determinations, they are advised that they may consider such factors as: (1) the witness's demeanor; (2) the witness's motives, biases, interests, and prejudices; (3) whether the witness is contradicted by prior inconsistent statements or by other evidence; (4) the reasonableness of the witness's testimony, in light of other evidence; and (5) any other factors that bear on believability. 3d Circuit Civil Pattern Jury Instruction 1.7 (Preliminary Instruction). Of course, unlike jurors, special masters provide reviewing courts the reasons for crediting the testimony of one witness over another and, unlike jurors, special masters develop expertise in weighing and evaluating expert testimony.

base their decisions on reliable evidence. *Daubert*, 509 U.S. at 594-96. *Daubert* provides a useful framework for evaluating scientific evidence in Vaccine Act cases. *Terran,* 41 Fed. Cl. at 336, *aff'd*, 195 F.3d 1302. *See also Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40 (2005) (special master performs gatekeeping function when he "determines whether a particular petitioner's expert medical testimony supporting biologic probability may be admitted or credited or otherwise relied upon").

The Vaccine Act clearly contemplates that the special masters will weigh the merits of the evidence presented in making entitlement decisions. Special masters are not bound by any particular "diagnosis, conclusion, judgment, test result, report, or summary," and in determining the weight to be afforded to these matters, "shall consider the entire record...". § 300aa–13(b)(1). Petitioners do not automatically shift the burden to respondent to prove alternate cause merely by offering an opinion of a medical expert. Respondent may challenge the factual underpinnings of a causation opinion, the validity of the opinion itself, or both. *See De Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1353-54 (Fed. Cir. 2008).

Special masters weigh the evidence found in the medical records (*see, e.g., Ryman*, 65 Fed. Cl. at 41-42); consider evidence of bias or prejudice on the part of a witness, affiant, or expert (*see, e.g., Baker*, 2003 U.S. Claims LEXIS 290 at *107("profit motive")); weigh opposing medical opinions and the relative qualifications of experts (*see, e.g., Epstein v. Sec'y, HHS*, 35 Fed. Cl. 467, 477 (1996) and *Lankford v. Sec'y, HHS*, 37 Fed. Cl. 723, 726-27 (1997)); examine medical literature, studies, reports, and tests submitted by either party (*see, e.g., Sharpnack v. Sec'y, HHS*, 27 Fed. Cl. 457 (1993), *aff'd*, 17 F.3d 1442 (Fed. Cir. 1994)); and may consider a myriad of other factors in determining the facts of the case and the mixed questions of law and fact that arise in causation determinations. Special masters decide questions of credibility, plausibility, reliability, and ultimately determine to which side the balance of the evidence tips. *See Pafford*, 451 F.3d at 1359 ("Notably, this court accords great deference to a Special Master's determination on the probative value of evidence and the credibility of witnesses").

Two specific concerns emerged during Dr. Shoenfeld's testimony. In spite of his 2006 book chapter, filed as Pet. Ex. 38,[137] in which he commented that most of the well-conducted studies do not support a causal relationship between immunizations and T1D (Tr. at 99), Dr. Shoenfeld opined that "there is a close relationship between the clinical overt diabetes mellitus and the two vaccines that [Mr. Hennessey]. . .received prior to this emerging of the disease." Tr. at 15-16. *See also* Tr. at 64A-68. Although he couched his change of opinion in terms of the epidemiologic studies not accounting for

[137] Y. Shoenfeld and M. Tishler, *Vaccines and Autoimmunity*, from THE AUTOIMMUNE DISEASES, 4th Ed., N. Rose and I. Mackay, *eds*., Elsevier Academic Press (Amsterdam, The Netherlands, 2006).

"recent" research on the protective effects of Vitamin D,[138] the research showing that protective effect against T1D was not recent.[139] Furthermore, he advanced no rational reason for concluding that Vitamin D supplementation was more likely found more frequently in one cohort of such studies, rather than in both cohorts–a necessary condition for a confounding effect.

Doctor Shoenfeld's opinions, expressed in peer reviewed medical literature,[140] that well-conducted epidemiological studies militated against vaccine causation, contrasted unfavorably with his opinions during the hearing that vaccines could trigger both the appearance of autoantibodies and overt clinical symptoms of T1D. It appeared to me that Dr. Shoenfeld was tailoring his opinion for his audience, thus violating the "same intellectual rigor test" for evaluating expert testimony set forth by the Supreme Court in *Kumho Tire,* 526 U.S. 137.[141] In other words, in writing in peer reviewed literature, Dr. Shoenfeld stated that the epidemiologic studies finding no evidence of a causal relationship between vaccinations and T1D were well-conducted and he appeared to accept their conclusions. However, in testimony in a specialized and largely unknown U.S. court proceeding, he was willing to state definitively that the hepatitis B vaccine can cause T1D, and that it did so in Mr. Hennessey's case, opining that the studies to the contrary were either defective or otherwise inapplicable to Mr.

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[138] Doctor Shoenfeld testified that vitamin D can prevent or slow down the disease process in autoimmune diseases. Tr. at 30, 128-31. He did not specify whether it was effective in preventing or slowing the β islet cell destruction in the prodromal phase of T1D.

[139] The filed studies concerning vitamin D supplementation were published in 1999 (EURODIAB, Res. Ex. CCC, Tab 31), 2001(Hypponen, Res. Ex. CCC, Tab 30) and 2003 (Stene 2003a). All of these studies predated Dr. Shoenfeld's 2006 publication referring to the lack of association between vaccines and T1D. Even assuming that Dr. Shoenfeld's book chapter was prepared a year or two before its publication, the vitamin D studies still predated it.

[140] In addition to his statements in Pet. Ex. 38 regarding the Hviid study and the lack of association between T1D and vaccines, Dr. Shoenfeld is also on record that there is insufficient evidence of an association between autoimmune diseases in general and vaccines. *See* A. Borchers, *et al.*, *Vaccines, Viruses, and Voodoo*, J. INVEST. ALLERGOL. CLIN. IMMUNOL. 12: 155-68 (2002), filed as Pet. Ex. 32 ("The existing evidence is insufficient to support a causal relationship between various vaccines and the development of autoimmune disease, especially since postmarketing surveillances have failed to detect an association between vaccination and increased evidence of autoimmune diseases."). *Id.* at 64. Doctor Shoenfeld was a co-author of this article.

[141] In *Kumho Tire*, the court indicated that a trial judge is obligated to ensure that the testimony of experts reflects "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152. I emphasize that experts, like other witnesses, are free to change their minds about previously expressed opinions. However, like other witnesses, experts who retreat from previously expressed observations or opinions may be impeached by their prior inconsistent statements. In evaluating a prior statement and testimony inconsistent with that statement, a trier of fact may consider the reasons for the changed opinion in evaluating the weight to be accorded to the testimony. Doctor Shoenfeld's stated reason for changing his opinion simply does not hold water.

Hennessey's specific case.[142]

A second reason for concern about Dr. Shoenfeld's testimony concerned Mr. Hennessey's first two HB A_{1c} test results. In essence, Dr. Shoenfeld downplayed the importance of these tests, commenting that there are "false positives" in such tests, without offering any evidence supporting his insinuation that Mr. Hennessey's two initial tests were in error. Given the degree of reliance the medical community accords the HB A_{1c} test to measure blood glucose levels over time, the concordance between the initial test and the second test several weeks later, and their significance in effectively refuting a causal role for the hepatitis B vaccinations in Mr. Hennessey's case, Dr. Shoenfeld's failure to offer more than passing commentary concerning the significance of these tests is inexplicable.

Aside from these two specific concerns with Dr. Shoenfeld's testimony, I found, in general, that respondent's witnesses were far more qualified to opine on T1D than Dr. Shoenfeld. Doctor Shoenfeld has strong qualifications in the field of autoimmune conditions in general, but Drs. Bercu, Maclaren, and Rewers have strong qualifications on T1D in particular. With regard to autoimmunity, Dr. Whitton's qualifications were as impressive as Dr. Shoenfeld's. A comparison of their filed publications convinced me that Dr. Whitton's focus is on the evidence, not on his theories. Doctor Shoenfeld's filed medical and scientific journal articles were largely literature reviews. They repeat the same case reports, reference the same animal studies, and treat speculation as proven fact. In considering Dr. Shoenfeld's publications and his opinions, the aphorism "if your only tool is a hammer, everything looks like a nail" leaps to mind. Because his focus is on molecular mimicry as an explanation for autoimmune diseases, he calls all autoimmune conditions the "same disease." This contrasts unfavorably with Dr. Whitton's healthy skepticism about what may, or may not, trigger autoimmunity and his focus on the evidence supporting or refuting the theories he considers. A comparison of the depth of detail in their answers in the testimony is equally illustrative. Doctor Shoenfeld tended to make sweeping statements; Dr. Whitton carefully focused his answers, and appropriately assisted the attorneys (and the special master) in focusing their questions.

Thus, to the extent the evidence was in conflict, I generally accepted the testimony of the pediatric endocrinologists about matters pertaining to T1D over that of

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[142] Doctor Shoenfeld implied that there was something unique about Mr. Hennessey that made the epidemiologic findings inapplicable to him, but he did not point to anything in particular that demonstrated such uniqueness. In contrast, Dr. Maclaren testified that there was nothing unique about Mr. Hennessey, his presentation, or his clinical course that would distinguish him from thousands of other children who develop T1D. It appeared that Dr. Shoenfeld was reasoning backwards to reach his conclusion–that because Mr. Hennessey developed clinically overt T1D after vaccination, something in Mr. Hennessey's genetic makeup caused him to respond to vaccines differently from the majority. This overlooks the fact that many of the epidemiologic studies focused on those at high genetic risk for T1D, but nevertheless failed to find any association between the T1D and vaccines.

Dr. Shoenfeld. To the extent that Drs. Whitton and Shoenfeld offered conflicting testimony on autoimmunity, or other matters in which both witnesses were experts, I looked to the nature of the testimony, the reasons advanced for it, the support found in the evidence filed, and the witnesses' demeanor to determine which testimony to credit.

D. Applying *Althen* and *Loving/Misasi*.

I have carefully considered Dr. Shoenfeld's testimony, expert report, and the accompanying medical literature, as well as all of the evidence offered by respondent. Based on the evidence as a whole, I conclude that petitioner failed to meet his burden to demonstrate by a preponderance of the evidence that his hepatitis B vaccines played a causal role in his development of T1D and celiac disease. Moreover, there is insufficient evidence established in this record to conclude that any vaccine precipitates either the autoimmune process or the clinically overt phase of T1D. I set forth below the evidence I found most compelling in coming to the conclusion that petitioner has not established a *prima facie* case.

Because this was an omnibus test case, evidence was adduced concerning whether vaccines can induce the initial autoimmune reaction resulting in β islet cell destruction, and whether vaccines can precipitate or accelerate the onset of insulin dependence. Although petitioner's Pre-Hearing Submission was unclear as to whether Mr. Hennessey's case involved the former, the latter, or both, it is now apparent, based on the vaccines identified as causal and Dr. Shoenfeld's testimony, that the theory in this particular case is the acceleration of underlying β islet cell destruction, which triggered the onset of clinical symptoms of T1D. In his post-hearing brief, petitioner alleged that the two hepatitis B vaccines he received in the fall of 1998 "caused him to suffer [T1D]." In the next sentence, he acknowledged that the evidence demonstrated a long latency period for T1D, and that "he may have had a subclinical IDDM disease process for years prior to his hep B vaccines...". Pet. Post-Hearing Br. at 1.

Based on the uncontroverted evidence of a long prodromal phase in T1D patients who develop the condition at Mr. Hennessey's age, the two hepatitis B vaccines could not have initiated Mr. Hennessey's β cell destruction. As they are the vaccines alleged to be causal, it is now clear that the causation theory alleged is one of significant aggravation.

1. Evaluating the Significant Aggravation Evidence.

a. Mr. Hennessey's Condition Prior to the Vaccines.

Petitioner has conceded the probability that he had autoantibodies to β islet cells at the time he received his first hepatitis B vaccine. Petitioner has also conceded that he (or his parents) noted the presence of clinically overt symptoms of T1D within two days of his second hepatitis B vaccine.

The process of T1D development is generally understood by the medical community to have a long preclinical phase, characterized by the presence of one or more autoantibodies and the slow destruction of the pancreatic β islet cells. In many, but not all, individuals who develop autoantibodies, the β islet cell destruction reaches a point at which the remaining cells are insufficient to produce enough insulin to transport sufficient glucose to muscles to sustain them. Because the β islet cells do not regenerate, at this point, the individual has T1D. Blood glucose levels continue a gradual rise, and if not diagnosed by routine testing and treated, diabetic ketoacidosis ensues, characterized by polyuria, polydypsia, ketone bodies in the urine, and dehydration. Diabetic ketoacidosis can progress to coma and death.

Petitioner appears to be arguing that because he did not have polydypsia and polyuria until November 19, 1998, he did not have T1D until then. Doctor Shoenfeld appeared to define diabetes as existing only when no insulin is produced by the body. Tr. at 56. However, Dr Maclaren indicated that deaths from diabetic ketoacidosis, the end-stage of T1D, have occurred when 70% of the insulin-secreting β islet cells were destroyed, and that at the 50-70% level of destruction, clinical symptoms manifest. Tr. at 160-61, 188.

Doctor Maclaren characterized Mr. Hennessey's presentation at diagnosis as "indicative of an advanced loss of insulin secreting pancreatic β cells." Res. Ex. RR at 4. Additionally, Drs. Rewers and Maclaren offered uncontradicted testimony that T1D is present when an individual presents with any of the following: (1) symptoms, such as weight loss, fatigue, polyuria, and polydypsia, accompanied by a high spot blood glucose or any urinary glucose test; (2) two or more high spot glucose readings[143] on different days; or (3) one HB A_{Ic} measurement in excess of 6.5-7.0%.[144] In other words, T1D need not be clinically overt in order for insulin dependence to exist and be diagnosed. Their testimony that T1D is diagnosed in the absence of clinical symptoms is buttressed by many of respondent's exhibits.[145] At the time of his diagnosis, not only did Mr. Hennessey have T1D, he was in a state of diabetic ketoacidosis, the end stage of a long

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[143] Doctor Rewers' testimony on this point can be interpreted one of two ways. He testified that, based on data from DAISY, children who have two fasting blood glucose readings over 125 on two different days or a post-glucose-challenge level of over 200 are diagnosed with T1D and placed on insulin therapy. Tr. at 277. It was unclear from his testimony whether one reading over 200 after a glucose challenge was sufficient for diagnosis. However, Dr. Maclaren testified that one single blood glucose reading of 200 is indicative, if not diagnostic, of diabetes and that either a fasting blood sugar over 125 or a reading over 200 after glucose challenge would be diagnostic. Tr. at 146, 203.

[144] Tr. at 203.

[145] *See, e.g.*, Bennett and Knowler, Res. Ex. P at 331 ("Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, and polyphagia, and in its most severe forms, with ketoacidosis or nonketotic hyperosmolarity, which, in the absence of effective treatment, leads to stupor, coma, and death. Often symptoms are not severe or may even be absent....Hyperglycemia sufficient to cause pathologic functional changes may quite often be present for a long time before the diagnosis is made." (emphasis added)).

disease process.

One of the textbook chapters filed by respondent discusses the "staging" of autoimmune T1D (Type 1A). Stage I is the genetic susceptibility. Stage II is the "trigger," the event that causes one monozygotic twin to develop autoimmunity while the other twin does not, in spite of their identical genetics. Stage III, active autoimmunity, is characterized by the presence of one autoantibody and the beginning of β islet cell loss. Stage IV is characterized by the presence of two or more autoantibodies and the loss of some insulin secretion capacity. Approximately 90% of the individuals who reach this point progress to insulin dependence within 10 years. Stage V is overt diabetes, with a β islet cell loss of 60-80%. Stage VI represents complete insulin dependence–the end of the diabetic honeymoon period and the complete loss of β islet cells. Eisenbarth, Res. Ex. Q, at 402-03 and figure 23.3. Given the time frame necessary for an HB A_{Ic} level to reach 12.1%, the expert testimony established that Mr. Hennessey was in Stage V at the time of his vaccination.[146]

Although petitioner appears to be contending that clinical symptoms are the point at which T1D exists, Dr. Shoenfeld's testimony, report, and other evidence offered no support for the onset of clinical symptoms as the demarcation point, after which insulin dependence exists.[147] To illustrate the fallacy in the argument that symptoms reflect the "actual onset" of T1D, consider an analogy to lung cancer. The first clinical symptoms of lung cancer may be a persistent cough accompanied by bloody sputum. The cough and blood precipitate a medical consultation, resulting in testing and diagnosis, but the patient had lung cancer long before the clinical symptoms appeared. If the patient had received a chest x-ray or other medical tests months earlier, the cancer would have been diagnosed earlier. In T1D, clinical symptoms certainly reflect insulin dependence,

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[146] The witnesses did not testify directly about Mr. Hennessey's staging. Although Dr. Shoenfeld testified that it was impossible to know if Mr. Hennessey was insulin dependent at the time of the initial hepatitis B vaccination, I find otherwise. I reject his testimony that the HB A_{Ic} results of 12.1% could reflect a high sugar diet (*see* Tr. at 89-91) over the period between his vaccination and his T1D diagnosis, as there was no evidence to suggest such a diet and the pediatric endocrinologists' testimony about post-prandial blood glucose levels indicated that an average level of 350 mg/dL of blood glucose was exceedingly high, one unlikely to be reached based on diet alone. That average blood glucose level necessarily reflected severely reduced insulin production. I conclude that Dr. Shoenfeld's testimony reflected either his relative unfamiliarity with the HB A_{Ic} test, as compared to clinicians such as Drs. Revers and Maclaren, who use it in their practice and research, or that he simply chose to opine in favor of vaccine causation, in spite of the contrary evidence provided by this test, which reflected the advanced loss of pancreatic β islet cells referred to in Dr. Maclaren's report. Res. Ex. RR at 4.

[147] Clearly, clinical symptoms are important. The onset of clinical symptoms often triggers the diagnosis, particularly when annual or periodic physical examinations do not include urine or blood glucose tests. For Vaccine Act purposes, the onset of clinical symptoms triggers the statute of limitations found in § 300aa-16(a)(2). One of the cases initially included with Mr. Hennessey's case in the diabetes omnibus grouping was dismissed based on statute of limitations issues using the onset of clinical symptoms as the triggering event. *See Nations v. Sec'y, HHS*, No. 03-2013V(Fed. Cl. Spec. Mstr. Sept. 19, 2006) (unpublished).

but T1D can be, and often is, diagnosed before any observable manifestations of the condition. Once the "tipping point" is reached–the point at which the body can no longer produce sufficient insulin–a person is dependent upon supplemental insulin, and "has" T1D. When a T1D diagnosis is made based on test results, rather than clinical symptoms, the test results become the "manifestation of onset" for statute of limitations purposes. § 300aa-16(a)(2).

Mr. Hennessey's T1D various symptoms began at different (and sometimes unspecified) times in the fall of 1998. His mother's affidavit places onset of increased fatigue–loss of his "hustle"–as occurring during the fall hockey season after the August tryouts. Pet. Ex. 8 at ¶ 3. She placed onset of the "classic" symptoms on November 19, 1998, which is completely consistent with the contemporaneous medical records.[148] Precisely when his weight loss began is more difficult to determine, but the loss of ten pounds by November 30, 1998, in a child who weighed only 88 pounds at the start of the school year (late August or early September, 1998), most assuredly did not happen overnight.

It is clear that Mr. Hennessey met the first diagnostic method listed above, that of symptoms plus spot glucose readings, on November 30, 1998. However, meeting the diagnostic criteria on that date does not preclude his meeting other diagnostic criteria on an earlier date. Although Mr. Hennessey did not have any other spot glucose testing during the fall of 1998 (the second method of diagnosis listed above), his HB A_{1c} reading on November 30, 1998 of 12.1%, standing alone, is strong circumstantial evidence that, had his doctor performed a spot glucose screening it would have been high. Had an HB A_{1c} test been performed on September 15, 1998, it would have been higher than 6.5-7.0%, the third diagnostic method. Doctor Rewers provided unrebutted testimony that it would take from six months to a year for Mr. Hennessey's HB A_{1c} rate to climb from a high normal level of 6% to the 12.1% level at the time of his diagnosis. Tr. at 169. The charts at Res. Tr. Ex. 2 (slides Dr. Rewers used to illustrate his testimony) contained data developed from DAISY that HB A_{1c} levels gradually rise for one to four years, while remaining in the normal range, before moving into the 6.5-7.0 level at which insulin therapy is initiated. Tr. 277-78.

However, there was other circumstantial evidence to indicate that Mr. Hennessey's remaining β islet cells were not producing enough insulin to sustain him by mid-September. That evidence included the HB A_{1c} level of 11.7% on December 16, 1998, the vision improvement noted on that same date, the amount of weight loss he experienced between starting school and his hospitalization, and the decline in his growth rate in the two years before his diagnosis. Because petitioner's Post-Hearing Brief (*see* pp. 48-50) evinces a fundamental misunderstanding of both the nature of HB

[148] Although I credit Dr. Rewers' testimony that more careful questioning of Mr. Hennessey about when the frequent urination began would likely have elicited an earlier onset date (Tr. at 279B), an earlier onset of polyuria is unnecessary to my factual determination that the onset of T1D occurred before the vaccinations.

A_{lc} tests and the significance of the 12.1% level found during Mr. Hennessey's hospitalization, the nature of this testing is addressed in some detail, below.

As the pancreatic β islet cells are destroyed, the ability to manufacture insulin is diminished. When enough cells are destroyed, the pancreas no longer produces enough insulin to transport all the glucose produced by digestion from the bloodstream to the tissues. In response, blood glucose levels rise. In most cases, the decline in insulin production and the concomitant rise in blood glucose levels happen gradually. Doctor Rewers pointed to an example of the husband of one of his employees, noting a gradual rise in blood glucose readings over a period of twelve years. Tr. at 163.

The gradual rise in blood glucose can be detected with repeated spot glucose testing. A spot glucose measures the glucose level at the time the sample is taken. That level can be influenced by the nature of recent food intake, exercise, and insulin production capacity. Spot glucose readings vary from day to day and even hour to hour. Diabetic patients chart several spot glucose readings daily in order to determine their level of glucose control (Tr. at 456B-457A), and they adjust their insulin intake based on those readings, their diet, and their activity level. *See, e.g.*, Pet. Ex. 5, p. 29 (adjusting Mr. Hennessey's insulin intake based on hockey camp and other factors).

In contrast, HB A_{lc} percentages are not reflective of any one spot reading, although they are derived from actual blood glucose levels. They are the biological equivalent of constant blood glucose monitoring, producing a reading that reflects an average of glucose levels over the preceding three to four months. Because it is an average, an HB A_{lc} percentage determined before insulin therapy begins reflects the insulin production capacity available in the patient in the two to four months before the test. A level in excess of 6.5-7.0% indicates that the individual's insulin production is insufficient to remove sufficient glucose from the blood to tissue without supplemental insulin.

Hemoglobin A_{lc} is formed when one type of hemoglobin combines with blood glucose (by glycosylation) in erythrocytes (red blood cells). Older red blood cells, having had more opportunities for glycosylation to occur, contain the most HB A_{lc}. Young erythrocytes (newly produced red blood cells) contain the least. As one of the filed medical journal articles[149] (cited in Pet. Post-Hearing Br. at 49) explained: "The actual HB A_{lc} concentration is a function of red cell half-life and the rate of HB A_{lc} synthesis, which in turn is determined by the blood glucose concentration." Koenig and Cerami, Res. Ex. AA, at 30. The authors of this early work on the utility of using HB A_{lc} levels to guide the treatment of T1D predicted that a severely hyperglycemic individual would have a very high HB A_{lc} level. When treated to lower the blood glucose, the rate of HB

[149] R. Koenig and A. Cerami, *Hemoglobin A_{lc} and Diabetes Mellitus*, ANN. REV. MED. 31: 29-34 (1980) ["Koenig and Cerami"], filed as Res. Ex. AA. This 1980 article appears to be one of the first proposals for using the HB A_{lc} levels to measure glucose control.

A_{lc} synthesis would fall abruptly, but the percentage of HB A_{lc} would not immediately decrease, because the red blood cells that had already synthesized HB A_{lc} would remain in circulation until their death. "Thus, a single HB A_{lc} measurement should reflect a patient's mean blood glucose concentration over the previous two to three months." *Id*. at 30. The authors then went on to describe how they validated this prediction. *Id.* at 30-31. Since this 1980 publication, the HB A_{lc} test has developed into a standard test, the results of which have been scientifically correlated with mean or average blood glucose levels over the prior three month period. Tr. at 457A-59. *See also* Res. Tr. Ex. 1 at 2. (chart correlating HB A_{lc} percentages with mean blood glucose). Based on Mr. Hennessey's 12.1% HB A_{lc} level at hospitalization, his mean or average blood glucose over the preceding two to three months was approximately 350 mg/dL. It was certainly lower than 350 mg/dL at the beginning of that period than it was at the end (571 mg/dL at diagnosis), but the level averaged 350 mg/dL.

The slow decline in Mr. Hennessey's HB A_{lc} level from 12.1% to 11.7% over a two week period when his blood glucose was under excellent control validates the testimony of both Drs Maclaren and Rewers that, at the time of Mr. Hennessey's initial hepatitis B vaccination, his HB A_{lc} level was in excess of the level required for diagnosis of T1D. Tr. at 170A-71A, 278A. Had a test been performed at that time, Mr. Hennessey would have begun insulin therapy immediately, and the diabetic ketoacidosis he experienced would not have occurred. As Dr. Maclaren testified, an HB A_{lc} test result of 6.5%, or approximately half of Mr. Hennessey's 12.1% result, would be diagnostic of diabetes. Tr. at 203.

In his post-hearing brief at 49, petitioner correctly quoted Koenig and Cerami, Res. Ex. AA, at 30, as stating that HB A_{lc} level does not correlate with occasional checks of fasting or postprandial blood glucose. However, the implication petitioner attempted to draw from this one statement, taken out of context, is incorrect. Without any support in the evidentiary record, petitioner asserted that it is not scientifically possible to use a single test result on November 30, 1998, to predict what Mr. Hennessey's blood glucose level would have been three months earlier. Pet. Post-Hearing Br. at 49. Other references in petitioner's post hearing brief to the HB A_{lc} test are equally, and more obviously, incorrect. Petitioner called the HB A_{lc} test "forward-looking." *Id.* It is not. It is a measurement of retrospective blood glucose levels, not prospective ones. While an individual's history of diabetes control may serve to predict how well he will control his blood glucose in the future, the HB A_{lc} test is an objective measurement of past control, not, as petitioner contended, a prediction of the future.

While noting that there were actually two HB A_{lc} tests, not a single one, within three months of Mr. Hennessey's initial hepatitis B vaccination, I agree that it is impossible to predict precisely what petitioner's blood glucose level was at any particular point in time in the three months preceding November 30, 1998. However, respondent's experts were not attempting to determine a precise blood glucose level at any single point in time; rather, they were using the well-established knowledge about HB A_{lc} levels and their rate of increase or decrease to demonstrate that, by mid-September, 1998, Mr.

Hennessey had an HB A_{Ic} level diagnostic of T1D. They persuasively testified that treating physicians routinely use one HB A_{Ic} test to determine the level of diabetic control–the average blood glucose level–over a three month period of time.[150] Their testimony is borne out by Mr. Hennessey's medical records. Although Dr. Kyllo's records occasionally mention Mr. Hennessey's own logs of his spot glucose readings (*see* Pet Ex. 5, pp. 9, 16), the laboratory tests in the records from her treatment are all HB A_{Ic} levels. *See* Pet. Ex. 5, pp. 5-8. Apparently, this treating physician considered the HB A_{Ic} tests a reliable indicator of glucose control.

Mr. Hennessey's blood glucose level of 571 mg/dL on November 30, 1998 (*see* Pet. Ex. 4, p. 3), was extremely high. His HB A_{Ic} level demonstrated an average blood glucose for the preceding three months of 350 mg/dL. These two blood glucose levels–one "spot" reading and one an average–are strong circumstantial evidence of a long period of increasing blood glucose due to insufficient natural production of insulin–a state of insulin dependence.

Based on their expertise as pediatric endocrinologists, clinicians, and research scientists, Drs. Maclaren and Rewers persuasively testified that a 12.1% HB A_{Ic} test on November 30, 1998, meant that Mr. Hennessey's HB A_{Ic} level on August 30, 1998, was over the level required for a diagnosis of T1D. The small decline of 0.4% in the two weeks after insulin therapy began compellingly supported their testimony. A huge reduction in spot blood glucose (from 571 mg/dL on November 30, 1998, to a spot reading of 169 mg/dL in mid-December, 1998 (*see* Pet. Exs. 4, p. 3, and 5, p. 12)), and generally good glucose control in the preceding two weeks, resulted in only a small decline in HB A_{Ic}. In March, 1999, three months after his diagnosis, and after three months of daily insulin therapy with spot glucose readings in the 80-180 mg/dL level (Pet. Ex. 5, p. 9), Mr. Hennessey's HB A_{Ic} level had only declined to 6.9% (*id.*). Although circumstantial, this evidence was compelling and utterly convincing as to Mr. Hennessey's diabetic condition at the time of his hepatitis B vaccines. I add that it was unrebutted by petitioner.

The HB A_{Ic} level was not the only piece of circumstantial evidence indicating that Mr. Hennessey's blood glucose levels were abnormal and reflective of insulin dependence at the time of his vaccination. Although blurred vision was not mentioned as a symptom during Mr. Hennessey's initial hospital stay, his vision was recorded as "improved greatly since getting better control of his diabetes" at the followup visit two weeks later, on December 16, 1998. Pet. Ex. 5, p. 12. Doctor Rewers explained that blurred vision is common in children who present with very high glucose levels and symptoms of polyuria and polydypsia. The blurred vision results from high blood glucose, which causes the lenses of the eye to swell. A sudden rise in blood glucose

[150] As Doctor Whitton testified: "In this case, Thomas Hennessey's hemoglobin A-1C was 12.1 percent. That's in Exhibit 5, page 1, I believe. And that reflects the findings. And it's physiological, it's biochemistry, it's quite clear. That must reflect the time period. He'd had high levels of blood glucose before he ever incurred the hepatitis B vaccine." Tr. at 347.

over a period of two weeks does not induce the same effect, although a two week period in which the blood glucose levels were controlled or normal would be sufficient for an improvement in vision to be noted. He explained that the vision problems develop slowly and reflect a period of three months or more of excessive blood glucose, but once the blood glucose is under control, the vision problems resolve more quickly. Tr. at 314-15. Doctor Rewers also opined that Mr. Hennessey's myopia, diagnosed at an eye examination in June, 1998,[151] reflected this slow process of lens swelling due to elevated blood glucose. Tr. at 313-15. This time frame is well within the six to twelve months necessary for the HB A_{Ic} level to rise from high normal to the 12.1% level.

Additional circumstantial evidence indicating that Mr. Hennessey's disease process had already advanced to insulin dependence at the time of his vaccinations is found in the 11% loss of weight he experienced between the start of the school year and his hospitalization. If, as Dr. Shoenfeld testified, the second vaccine supplied the "boost" that precipitated a very accelerated onset of clinically overt T1D (Tr. at 65), Mr. Hennessey's weight loss would have occurred at the rate of 3/4 pound per day between the second vaccination and his diagnosis. A weight loss that rapid certainly would have been noted. Additionally, I note that testimony that his rate of growth slowed in the two years preceding his diagnosis is consistent with the gradual loss of insulin production capacity over months to years. Insulin is a growth hormone, the lack of which retards growth. Tr. at 164-65.

Although unknown to Mr. Hennessey, his parents, or the health care provider who administered his hepatitis B vaccines, Mr. Hennessey was insulin-dependent[152] at the time of his initial hepatitis B vaccine. Even though he was not receiving insulin at the time and displayed no overt symptoms (except, perhaps fatigue and weight loss), he met the diagnostic criteria for insulin dependence because his remaining β islet cells could no longer produce enough insulin to keep his blood glucose levels in the normal range.[153] Thus, the timing of his vaccines, in Dr. Whitton's words, excludes a cause and effect relationship with his T1D. Tr. at 347, 376-77. *Accord*,Tr. at 282 (testimony of Dr. Rewers) and Tr. at 171A (testimony of Dr. Maclaren).

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[151] Doctor Rewers' testimony was based on a poorly copied medical record. Pet. Ex. 7, p. 1. At the hearing, the month of the vision examination could not be determined from that record, but it appeared to be either June or August of 1998. A better copy was subsequently filed, and the date was determined to be June, 1998.

[152] As noted earlier in this opinion, one of the terms used to describe T1D is "insulin dependent diabetes mellitus" or IDDM.

[153] Doctor Maclaren testified that most cases of T1D are diagnosed before ketoacidosis occurs, based on routine blood or urine testing. Tr. at 147A.

b. Mr. Hennessey's Condition After the Vaccines.

Within two days of his second hepatitis B vaccine, Mr. Hennessey was clearly in a worse clinical condition than he was prior to the initial hepatitis B vaccine. Equally clearly, his spot blood glucose levels were far worse at the time of his diagnosis than they would have been at the time of either his initial or second hepatitis B vaccine. He was in diabetic ketoacidosis, an extremely serious medical condition, at the time of his diagnosis on November 30, 1998.

c. Comparison of Mr. Hennessey's Condition Before and After the Vaccines.

Petitioner has the burden to demonstrate, in the language of the statute, "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). Whether, initially at least, he has met that burden depends on what is being compared. If the comparison is clinical symptoms, then Mr. Hennessey was clearly worse on November 30, 1998 than he was on September 15, 1998. If, on the other hand, the comparison involves the condition from which he suffers, rather than the clinical symptoms, Mr. Hennessey was insulin dependent on both dates, albeit undiagnosed and relatively asymptomatic on the earlier date. To return to the lung cancer hypothetical, the victim had the same disease on both dates, but was symptomatic only on the later.

Although the focus on the actual condition is both logical and medically correct, I am bound by the plain language of the statute. Mr. Hennessey clearly experienced a substantial deterioration in his health between mid-September and late November, 1998. However, I also find that the change in Mr. Hennessey's condition was not due to the administration of the vaccines, but rather to the natural progression of insulin dependence. I address this in greater detail, below.

2. Evaluating the Causation Evidence.

a. A Reliable Medical Theory.

Doctor Shoenfeld presented a medical theory that the hepatitis B vaccine, or some component of the vaccine, accelerated the autoimmune process of β islet cell destruction in Mr. Hennessey. He proposed several biologic models, including molecular mimicry or bystander effect, by which that specific autoimmune destruction could be initiated, but was less than clear in his theory of how the ongoing destruction could be aggravated by a vaccine.

Recognizing the long latency or prodromal period in T1D, Dr. Shoenfeld acknowledged that Mr. Hennessey likely had autoantibodies to insulin or β islet cells at the time his first hepatitis B vaccine was administered. Tr. at 65-67, 82. Thus, under his

molecular mimicry, bystander effect, or other theories, something in the initial hepatitis B vaccine began another autoimmune reaction that also targeted those same cells and the second vaccine then accelerated the destructive process. Alternatively, Dr. Shoenfeld argued that the vaccines activated the immune system and this activation itself increased the rate of autoimmune destruction. In other words, the two hepatitis B vaccines, simply by activating the adaptive immune system,[154] stirred a leisurely attack into a more frenzied one. Under this alternate theory, there need not be any degree of homology between the vaccine, or any component of it, and the β islet cells.

Whether either of these theories (or any others advanced by Dr. Shoenfeld) reach the degree of reliability necessary under *Daubert* is open to debate. I found much of Dr. Shoenfeld's testimony to be highly speculative. His testimony was predicated on his viewpoint that all autoimmune diseases are the same disease and, therefore, what can cause one autoimmune disease can cause any other autoimmune disease.

I carefully reviewed the publications that accompanied his report, many of which he authored or co-authored. Citing primarily to case reports, he and his co-authors repeatedly promoted at least part of the theory he advanced in this case. What was missing from his references was any support for his testimony that all autoimmune diseases are the same disease.

I did find support for the proposition that specific viruses or vaccines may cause or trigger some autoimmune diseases, but the process by which they do so has not been established. For example, measles virus may cause a condition known as idiopathic (immune) thrombocytopenia purpura ["ITP"]. Tr. at 50. The Vaccine Injury Table includes ITP as a condition associated with measles virus-containing vaccines. 42 C.F.R. § 100.3(v)(A). However, Dr. Shoenfeld did not assert that ITP could be caused by any virus or viral vaccine. Many of his own writings, and those of others that he relied upon, suggested that the hepatitis B vaccine, in particular, was associated with more autoimmune reactions than other vaccines. However, when studies (as opposed to case reports) of vaccines and autoimmune diseases were discussed in Dr. Shoenfeld's articles, those studies uniformly found no association between the hepatitis B vaccine and increased incidence of autoimmune disease in vaccinees versus controls.[155] It is

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[154] Doctor Whitton testified that the hepatitis B vaccine is not recognized by the innate immune system. Tr. at 442B, 444B.

[155] In a citation in a 2002 editorial, Dr. Shoenfeld stated that the Hib vaccine had been linked to T1D. *See* Y. Shoenfeld, *et al.*, *Vaccination as an additional player in the mosaic of autoimmunity*, CLIN. EXP. RHEUMATOL. 18: 181-84 (2000), filed as Pet. Ex. 28, at 181. He cited two of his own publications, both of which were filed as exhibits in this case, as support for this statement. *See* Y. Shoenfeld, *et al.*, *Vaccination and Autoimmunity - "Vaccinosis': a Dangerous Liaison?* J. AUTOIMMUNITY 14: 1-10 (2000), filed as Pet. Ex. 26, and A. Cohen and Y. Shoenfeld, *Vaccine-induced Autoimmunity*, J. AUTOIMMUN. 9: 699-703 (1996), filed as Pet. Ex. 25. The article filed as Pet. Ex. 25 only lists the mumps vaccine as having a reported relationship to T1D (and that citation lists a 1986 article as support). In the lengthy list of exhibits filed by both parties, I did not find any other articles supporting a mumps-T1D link. Of more concern is the

worth noting that none of Dr. Shoenfeld's own peer reviewed publications linked vaccines to T1D, although he occasionally mentioned the Classen studies. *See, e.g.*, Molina and Shoenfeld, Pet. Ex. 37. In this exhibit's relatively recent and lengthy literature review, T1D is not mentioned as an autoimmune condition associated with vaccinations.

Petitioner has set forth a medical theory [156] that vaccines in general, and the hepatitis B vaccine in particular, may trigger the onset of autoimmune destruction of β islet cells and may significantly aggravate subclinical T1D. He has not established that the theory is a reliable one. *See Knudsen*, 35 F.3d at 548 (the logical sequence of cause and effect "must be supported by a sound and reliable medical or scientific explanation").

b. Logical Connection.

Mr. Hennessey has also failed to establish any logical connection between his hepatitis B vaccinations and his T1D. The evidence that he already had diagnosable, albeit undiagnosed, T1D at the times the vaccines were administered is overwhelming. Likewise, the evidence that the natural progression of insulin dependence, rather than his vaccines, was responsible for his diabetic ketoacidosis is also overwhelming.

Without reiterating the lengthy discussion of epidemiologic evidence failing to find a connection between vaccines in general, and the hepatitis B vaccine in particular, in either initiating autoantibodies or precipitating the onset of overt clinical symptoms, I found such evidence to be highly relevant and persuasive on the general causation question. Epidemiologic studies can be probative evidence relevant to causation. *Grant*, 956 F.2d at 1149.

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reference to Hib vaccine and T1D in the other supporting citation, Pet. Ex. 26. It includes a section on diabetes and immunization. *Id*. at 5-6. After a very brief citation to Dr. Classen's largely discredited work, Dr. Shoenfeld next discussed the large studies that failed to find any statistical link between T1D and Hib in general, or in timing. He also included a paragraph that discussed the Johns Hopkins workshop (found at Res. Ex. CCC, Tab 98), which came to the conclusion that "no vaccines have been shown to increase the risk of diabetes type I in humans." (quoted in Pet. Ex. 26 at 5-6). Yet, Dr. Shoenfeld cited this article for the proposition that the Hib vaccine and T1D had been linked. Although technically correct, the reference is misleading, as most of the section covered studies that had refuted Dr. Classen's purported "link."

[156] For purposes of this decision, I need not decide whether molecular mimicry allegedly caused by a viral infection or a virally-based vaccine remains a plausible theory. I found Dr. Whitton's testimony on the lack of evidence for molecular mimicry at work in humans after viral infection to be highly persuasive. *See* Tr. at 385A-86A (testifying that the only example of molecular mimicry at work in human disease, found after decades of searching, is the role of streptococcus bacteria in causing rheumatic fever, and calling the evidence for molecular mimicry's role in other autoimmune diseases "extraordinarily weak"). I note that Dr. Whitton's testimony was consistent with the conclusions of the 2002 IOM report on immunizations and autoimmune disease. *See* Res. Ex. CCC, Tab 97, at 17.

With regard to specific causation, epidemiology is not dispositive. *Grant*, 956 F.2d at 1149. However, there is a dearth of evidence that suggests Mr. Hennessey was atypical, and therefore that such evidence is inapplicable to him.[157] I note that the more recent prospective cohort studies, including DAISY and the European studies have focused on children with high genetic risk for T1D, those with a family history of T1D, and normal controls. They have not found any indication that vaccines affect T1D rates in any of these groups.

Even disregarding the cohort studies refuting a connection between T1D and vaccines, I considered the following evidence highly persuasive in concluding that there is no connection, logical or otherwise, between Mr. Hennessey's two hepatitis B vaccines and his T1D: (1) Mr. Hennessey's HB A_{Ic} level strongly indicated that he was insulin dependent at the time he received his first hepatitis B vaccine; (2) there is no reliable evidence that the hepatitis B virus causes either production of autoantibodies or precipitates clinically overt T1D; (3) there is no evidence that either the aluminum adjuvant or thimerosal causes autoimmune reactions or precipitates clinically overt T1D; and (4) a third hepatitis B vaccine had no apparent effect on Mr. Hennessey's remaining insulin-producing β islet cells.

Doctor Shoenfeld's opinion on causation cannot bridge the gap created by the evidence in this case. As the Supreme Court commented in *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997): "A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." That is my conclusion here. Petitioner has failed to demonstrate a logical connection between Dr. Shoenfeld's theories and his T1D.

c. A Proximate Temporal Relationship.

There are two timing issues presented in the general causation case: (1) the appropriate temporal relationship between vaccinations and the initiation of β islet cell autoantibodies and (2) the postulated "second hit" that might precipitate the onset of clinical symptoms of T1D by causing an accelerated rate of β islet cell destruction. In Dr. Shoenfeld's somewhat wandering and unfocused testimony on timing (*see* Tr. at 51-55), the distinction between these two time frames was blurred. Because Mr. Hennessey has not based his claim for compensation on any of his early childhood vaccines precipitating the autoimmune process, I do not address the timing of his early vaccinations.

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[157] Doctor Maclaren directly addressed this uniqueness claim: "If we're saying okay, then it must be that Mr. Hennessey was a rare, peculiar individual very different from the rest of the patients. I see no evidence for that as his onset looks typical. His association with celiac disease was just the same, so why should he be considered different and not just ordinary and vanilla flavored Type I diabetes like all of my other patients?" Tr. at 180.

Doctor Shoenfeld postulated several periods for the medically appropriate temporal relationship between vaccine and disease. He first described the time frame appropriate between vaccine and the initiation of T1D autoantibodies and the beginning of the β islet cell destruction, then turned to the role a vaccine would play in the acceleration of that destructive process. Although only the latter time frame is implicated in Mr. Hennessey's specific case, I address both time frames below because other omnibus cases may reflect the former theory.

(1) Initiation of Autoimmune β Cell Destruction.

Doctor Shoenfeld indicated that, in order to consider a vaccine causal, most experts in the field would expect to see an autoimmune reaction between three and six weeks after vaccination. Tr. at 51. He explained that the immune system (referring to the adaptive immune system) responds in about three weeks, and another week would be needed to see the immune reaction. Tr. at 51-52. He then indicated that, based on more recent research demonstrating that in many autoimmune diseases, autoantibodies are present for years prior to the onset of clinical symptoms, two years between a vaccination and the onset of clinical symptoms would not be inappropriate. He also noted that, because of intervening environmental factors, it would be difficult to determine that a vaccine was causal after that period of time. Tr. at 52-53.

Doctor Shoenfeld was not specific about when he would expect to see the appearance of autoantibodies, following a precipitating vaccine. If the autoantibodies are the autoimmune reaction to which he was referring, then the three to six week window would apply. The longer period (two years) would apply to the onset of clinical symptoms, rather than the appearance of autoantibodies. Doctor Maclaren's testimony was that β islet cell autoantibodies almost always appear in early childhood, and that it is rare to see them develop in a child older than six years of age. Tr. at 161-62.

(2) Acceleration of the Autoimmune β Cell Destruction (Significant Aggravation Theory).

With regard to the postulated "second hit," Dr. Shoenfeld's testimony on timing remains unclear, largely because he did not carefully identify the symptoms to which he was referring. Having already addressed the issue of whether Mr. Hennessey was already insulin-dependent at the time of the first hepatitis B vaccine, I will not reiterate that evidence here.

In the case of an acceleration of the autoimmune process of β islet cell destruction in T1D, Dr. Shoenfeld testified that two weeks might be a sufficient time period for either an initial or second dose of a vaccine to precipitate overt clinical symptoms. Tr. at 54. He did not specify what clinical symptoms he might expect to see. The period might be even as long as six to eight weeks. Tr. at 55. As he testified, in the move from subclinical to overt T1D, Dr. Shoenfeld "relied on the short period, other than a long period of induction." Tr. at 66.

In response to my questions, he clarified his earlier testimony. In the case of a vaccine administered for the first time, he testified that it would take more than three weeks to precipitate a "reaction." Tr. at 117. A reaction to a second vaccine could occur within two weeks, and with a third vaccine, the reaction might occur within days or even hours. Tr. at 116-18.

The weight of the evidence is that Mr. Hennessey was experiencing subtle symptoms of T1D within a month of his initial vaccine (the loss of his "hustle" and his weight loss since starting school).[158] This would be within the time period Dr. Shoenfeld found appropriate, but it did not appear from the testimony that these were the symptoms Dr. Shoenfeld meant. His testimony referenced the onset of clinically overt symptoms (Tr. at 15-16) such as polydypsia and polyuria, which began over eight weeks after the initial vaccination, or outside the six to eight week time frame. Perhaps for that reason, Dr. Shoenfeld's testimony focused primarily on the second vaccination, stating that the first vaccine "accelerated the disease to a degree" and the second one caused "a very accelerated process." Tr. at 65.

In discussing the temporal relationship between the second vaccination on November 17, 1998, and clinical symptoms, Dr. Shoenfeld's testimony was undercut by his imprecision. Doctor Shoenfeld testified that Mr. Hennessey had symptoms two weeks after his second vaccination, apparently referring to the symptoms experienced at the time of his doctor's visit on November 30, 1998. However, based on his mother's affidavit and the contemporaneous medical histories, Mr. Hennessey began experiencing clear symptoms of T1D (polydypsia and polyuria) by November 19, 1998, or within two days of his second vaccination, a reaction too quick, based on Dr. Shoenfeld's testimony about reaction to a second dose of a vaccine. Based on the "several weeks" history of polyuria at the doctor's visit, the polyuria likely predated the second vaccination. Tr. at 196-97.

With regard to the third vaccine, there was no apparent effect on his remaining β islet cells, as he remained in his diabetic honeymoon period for some months thereafter.

Doctor Shoenfeld did not cite to any support for his testimony about biologically or medically appropriate time frames between a precipitating event and the onset of clinically overt T1D, and nothing in the literature filed supported his testimony with regard to T1D. The time frames to which he testified, three to eight weeks for an autoimmune reaction to a first vaccination, and lesser time periods for a second or third, appear biologically appropriate for autoimmune diseases in general, but not for T1D in particular.

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[158] Some of the symptoms may have begun even earlier, as Ms. Hennessey's affidavit was not clear about when either hockey tryouts or school began.

(3) Evidence Rebutting Dr. Shoenfeld's Timelines.

The testimony of respondent's experts established that T1D presents differently from other autoimmune diseases. Because of the many prospective cohort studies conducted worldwide, there is a wealth of information concerning autoantibodies and clinically overt disease that is not available in many, perhaps even most, other autoimmune conditions. Identification of high risk genetic backgrounds and newborn screening for the at-risk genes has identified a population of newborns for these prospective studies. Pediatric endocrinologists such as Dr. Rewers and Dr. Maclaren have 20-25 years of experience with T1D predictive algorithms, and, thus, a more sophisticated understanding of the natural progression of individuals from autoantibody positive status to clinically overt disease.

Based on that wealth of experience, Dr. Maclaren opined the timing of the events in Mr. Hennessey's case precluded a cause and effect relationship between his vaccinations and his T1D. Tr. at 141. Although some very young children experience a rapid onset of T1D, in older children and adults, the time period between the appearance of the first autoantibody, usually between nine months and three years of age, and onset of clinical symptoms is measured in years. Tr. at 159-64. In this slow progression to clinically overt T1D, there is no requirement for any precipitating event. Doctor Rewers concurred, indicating that the slow progression to T1D seen in children who develop clinically overt T1D at Mr. Hennessey's age at diagnosis, occurs over a period of years, and that the two months postulated by Dr. Shoenfeld was simply too short a period of time. Doctor Rewers explained that the rate of progression from autoantibody positive to T1D diagnosis is dependent on the genetic makeup of the children. Tr. at 270-71A, and only enteroviral infections appear to move the individuals who have two or more autoantibodies faster along the path to T1D. Tr. at 271A. The older a child is at T1D diagnosis, the longer the preclinical period. Tr. at 273.

Considered as a whole, the evidence does not support a biologically appropriate time frame between Mr. Hennessey's vaccinations and his development of T1D. Doctor Shoenfeld's theories regarding biologically appropriate time frames between trigger and onset of autoimmunity may well be appropriate for other autoimmune diseases, but these time frames conflict with the pathophysiology of the progression from autoimmunity to T1D. Tr. at 281-82.

Petitioners have the burden to demonstrate the existence of a "scientific temporal relationship." *Pafford v. HHS*, 64 Fed. Cl. 19, 29-30 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). The time frame must be medically acceptable. *De Bazan*, 539 F.3d at 1352. Because Dr. Shoenfeld's testimony on temporal relationships is contrary to what is known about the pathophysiology of T1D, I conclude that petitioner has failed to establish *Althen's* third prong in this case.

E. Alternate Cause.

Because I have concluded that petitioner has not established a *prima facie* case that his vaccines significantly aggravated what he characterized as his "pre-diabetic" status, the burden of proof never shifted to respondent to establish an alternate cause for petitioner's illness. However, respondent did advance alternate explanations for petitioner's condition, and therefore, I assess the evidence proffered on these issues.

Two aspects of alternate cause were raised by the evidence regarding T1D. First, that the precipitating event in Mr. Hennessey's insulin dependence was an enteroviral infection, not his vaccines, was addressed directly in respondent's post-hearing submissions. The other aspect of alternate cause pertains to the significant aggravation analysis. As respondent's post-hearing submissions were made prior to Judge Lettow's decision in *Loving*, respondent's arguments concerning the reason for the change in Mr. Hennessey's condition between vaccination and diagnosis were set forth, but not within the *Loving* framework. They were, nevertheless, raised in both evidence and argument. I address the "alternate trigger" issue first.

1. Enteroviral Infection as a Trigger of Insulin Dependence.

Respondent presented logical and compelling evidence that Mr. Hennessey's July, 1998, physician's visit was prompted by an enterovirus infection. Although no tests for the virus were performed, circumstantial evidence, including the timing (a "summer cold"), the nature of the symptoms, and the lack of any conjunctivitis, strongly suggested an enteroviral etiology. Given the slow nature of the progression of β islet cell destruction, the timing of this illness makes it far more likely as a "trigger" of Mr. Hennessey's insulin dependence than his vaccinations in September and November, 1998. Unlike the hepatitis B vaccine, there is some evidence suggesting that enteroviral infections in the three to six months before onset of insulin dependence may precipitate that onset. It is not clear, however, whether the enteroviral infections merely accelerate the process in children who would have become insulin dependent a month or two later, or whether they cause insulin dependence in children who would have remained in the pre-clinical plateau for years or decades longer.

The role of enteroviruses in the period preceding the development of islet autoimmunity is the subject of a number of studies, but, even if their presence is established, enteroviruses may not play a causal role in the development of clinically overt symptoms. Any association may represent a common genetic susceptibility to both these viruses and to β islet cell destruction, rather than a causal role.

Doctor Rewers testified that enteroviruses are the primary infectious candidate investigated in the TEDDY study. There is a broad body of literature suggesting their role as initiators or triggers of clinically overt T1D. According to Dr. Rewers, an enterovirus infection is a far more likely candidate to be the "straw that broke the camel's back" than the hepatitis B vaccine. Enteroviruses, in the form of "summer colds" strike

from late June through September, the appropriate time frame to account for the seasonal variation in diagnosis of clinically overt T1D. There are no other major viruses that are prevalent at that time of year. Studies from Finland and Sweden indicate that enteroviruses can either precipitate the development of autoantibodies or push someone with those antibodies over the precipice into clinically evident diabetes. Tr. at 253-56.

I emphasize that I found Dr. Rewers to be a highly qualified and highly credible witness. However, I find that some of his opinions on the enteroviral infection as an alternate cause were based on unpublished and non-peer reviewed data. Moreover, it was data I have not had the opportunity to review. Thus, I conclude that, while it was far more likely that the July infection constituted the "straw that broke the camel's back" than the vaccines in Mr. Hennessey's case, neither the infection nor the vaccines rise to the level of preponderant evidence. Having already concluded that petitioner has failed to establish a *prima facie* case for causation, respondent's failure to demonstrate alternate cause has no legal (or practical) effect.

I further observe that it does not appear that a precipitating factor is necessary in the shift in an individual's state from autoantibody positive to insulin dependence. A review of the studies filed in this case demonstrate that many individuals are diagnosed with insulin dependence without any precipitating event. Precipitating events–the so-called "second hit"–were postulated, based on some evidence of increased infections in the months immediately preceding T1D diagnosis. They did not occur in all, or even most, children with T1D.

2. Alternate Cause for the Significant Aggravation of Mr. Hennessey's Condition.

One of the issues left open in the *Loving* test is the nature of petitioner's burden with regard to demonstrating that a vaccine caused an actual change for the worse, versus the natural progression of the underlying injury, disease, or condition. In this respect, *Misasi* may be a clearer formulation of where the burdens of proof lie, at least in the off-Table claim. *Misasi* requires the same first two steps as in *Loving*, but the third and fourth steps differ, with *Misasi* requiring, as step three in the analysis, a prediction of what the vaccinee's condition would have been, had the vaccine not been administered, and as step four, a comparison of the current condition with the predicted condition. *Misasi*, 23 Cl. Ct. at 324. Exactly who has the burden to demonstrate what the petitioner's condition would have been, but for the vaccine, remains somewhat amorphous. To meet the significant factor and but for tests set forth in *Shyface*, 165 F.3d at 1352, the burden would appear to be petitioner's. That is, in order to demonstrate that the vaccine was a significant factor in, and a but for cause of, Mr. Hennessey's condition on November 30, 1998, it would appear that petitioner must show the vaccine, and not the natural progression of the preexisting condition, was responsible. To do otherwise would be to impermissibly shift the burden of proof to respondent to demonstrate that something other than a vaccine was responsible for Mr. Hennessey's T1D.

However, even analyzing the evidence in terms of alternate cause and thus placing the burden on respondent to show what petitioner's condition would have been, I am convinced by overwhelming evidence, that Mr. Hennessey's condition on November 30, 1998 was the result of the state of β islet cell destruction that existed on (and before) September 15, 1998. Diabetic ketoacidosis does not occur overnight. It is the result of gradually increasing insulin levels over time, resulting from, in Mr. Hennessey's case, insulin dependence that existed prior to receipt of any vaccine. Even though I conclude that respondent did not have the burden to do so, respondent demonstrated by preponderant evidence that Mr. Hennessey's worsened condition after receipt of the two hepatitis B vaccines was the result of the natural progression of insulin dependence, not the vaccines.

F. Celiac Disease.

Petitioner based his celiac disease claim on his T1D claim. Because I have concluded that he failed to demonstrate vaccine causation of his T1D, the celiac disease claim necessarily fails. With regard to Mr. Hennessey's celiac disease, respondent established an alternate cause for the condition--exposure to gliadin, from wheat products, in a genetically susceptible individual. The overwhelming weight of the evidence is that gliadin exposure is the only trigger for celiac disease.

Mr. Hennessey's positive screening test result occurred 11 months after his last hepatitis B vaccine, and 13 months after his T1D diagnosis. Doctor Shoenfeld could not establish when the celiac disease began, although it had been in process at some point prior to the endoscopy. If, as Dr. Shoenfeld's expert report suggests, the T1D caused the celiac disease (or the same autoimmune process caused both)–a fact not established by the evidence–there is no evidence that the timing of onset meets Dr. Shoenfeld's criteria.

V. Conclusion.[159]

Petitioner has not demonstrated by a preponderance of the evidence that his condition was significantly aggravated by the hepatitis B vaccinations he received on September 15 and November 17, 1998. He has thus failed to establish his case for compensation and the petition for compensation is therefore DENIED. In the absence of

[159] Based on the evidence and the causation conclusions drawn from it in this test case, appropriate orders will be issued in the other T1D omnibus cases. In most of those cases, the evidentiary record is relatively complete, but the parties will be permitted to supplement it with any missing medical records relevant to causation, case-specific expert reports, or other evidence. If hearings are needed, counsel should anticipate that they will be held expeditiously.

a motion for review filed pursuant to RCFC, Appendix B, the clerk is directed to enter judgment accordingly.[160]

IT IS SO ORDERED.

s/ Denise K. Vowell
Denise K. Vowell
Special Master

[160] Pursuant to Vaccine Rule 11(a), entry of judgment can be expedited by each party's filing a notice renouncing the right to seek review.