IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS
No. 01-162V
Filed: February 12, 2009
To Be Published

COLTEN SNYDER, by and through KATHRYN SNYDER and JOSEPH SNYDER, his natural guardians and next friends	*	Omnibus Autism Proceeding; Autism Spectrum Disorder, Pervasive Developmental Disorder, Causation, Measles, MMR, Mercury, Thimerosal, Waiver Applying *Daubert,* Weight of Expert Opinions, Credibility of Witnesses
Petitioners,	*	
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Christopher W. Wickersham, Sr., Esq., Lloyd Bowers, Esq., and Thomas B. Powers, Esq., for petitioners.

Alexis S. Babcock, Esq., Katherine Esposito, Esq., Voris Johnson, Esq., and Vincent Matanoski, Esq., U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Vowell, Special Master:

On March 22, 2001, Kathryn and Joseph Snyder ["petitioners"] filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C.

[1] Vaccine Rule 18(b) provides the parties 14 days to request redaction of any material "(i) which is trade secret or commercial or financial information which is privileged and confidential, or (ii) which are medical files and similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." 42 U.S.C. § 300aa12(d)(4)(B). Petitioners have waived their right to request such redaction. *See* Petitioners' Notice to Waive the 14-Day "Waiting" Period as Defined in Vaccine Rule 18(b), filed December 2, 2008. Respondent also waived the right to object to the disclosure of information submitted by respondent. *See* Respondent's Consent to Disclosure, filed January 14, 2009. Accordingly, this decision will be publicly available immediately after it is filed.

§ 300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"], on behalf of their minor son, Colten Snyder ["Colten"], alleging that the measles, mumps, and rubella ["MMR"] vaccination Colten received on April 23, 1998, caused a "post-vaccinal encephalopathy." Petition, ¶ 9. Subsequently-filed documents have clarified the nature of the injury claimed. Petitioners now allege that a combination of thimerosal-containing vaccines ["TCVs"] and the measles component of the MMR vaccine caused Colten to develop a pervasive developmental disorder ["PDD"], a term which is sometimes used synonymously with the term autism spectrum disorder ["ASD"]. *See* Petitioners' Prehearing Memorandum ["Pet. Prehearing Memo"] at 3.

To be eligible for compensation under the Vaccine Act, a petitioner must either demonstrate a Vaccine Table[3] 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). The petitioners in this case do not contend that Colten suffered a "Table" injury. Therefore, in order to prevail, they must demonstrate by preponderant evidence: "(1) a medical theory[4] 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).

After considering the record as a whole, I hold that petitioners have failed to establish by preponderant evidence that Colten's condition was caused or significantly aggravated by a vaccine or any component thereof. The evidence presented was both voluminous and extraordinarily complex. After careful consideration of all of the evidence, it was abundantly clear that petitioners' theories of causation were speculative and unpersuasive. Respondent's experts were far more qualified, better supported by the weight of scientific research and authority, and simply more persuasive on nearly every point in contention. Because of pervasive quality control problems at a now-defunct laboratory that tested a key piece of evidence, petitioners

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[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.

[3] 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.

[4] Doctor Wiznitzer, one of the expert witnesses, explained that scientists use the terms "hypothesis" and "theory" with very specific meanings. A hypothesis is an idea proffered to explain an event. A theory is what is developed after a hypothesis has been subjected to many attempts to disprove it, and thus, it is likely correct. Cedillo Tr. at 1632, 1731A-35. This is an important distinction, but because much case law and many of the witnesses in this case have used the two terms as if they were interchangeable, I do likewise.

could not reliably demonstrate the presence of a persistent measles virus in Colten's central nervous system. Petitioners failed to establish that measles virus can cause autism or that it did so in Colten. They failed to demonstrate that amount of ethylmercury in TCVs causes immune system suppression or dysregulation. They failed to show that Colten's immune system was dysregulated. Although Colten's condition markedly improved between his diagnosis and the hearing, the experimental treatments he received cannot be logically or scientifically linked to the theories of causation. Given the advice that petitioners received from a treating physician, Colten's parents brought this action in good faith and upon a reasonable basis. However, they have failed to demonstrate vaccine causation of Colten's condition by a preponderance of the evidence. Therefore, I deny their petition for compensation.

Colten's case was heard as part of the largest omnibus proceeding in the history of the Vaccine Act. It was one of three test cases on the first of two theories[5] of causation ["Theory 1"] advanced by petitioners in the Omnibus Autism Proceeding ["OAP"]. Theory 1 is that a combination of the MMR vaccine and TCVs, acting in concert, cause some ASDs. The other two cases involving Theory 1 are *Cedillo v. Sec'y, HHS*, 98-916V, and *Hazlehurst v. Sec'y, HHS*, 03-654V.

A brief history of omnibus proceedings under the Vaccine Act in general, and of the autism cases in particular, is necessary to explain what constitutes the "record as a whole"[6] upon which this case was decided. That history is set forth in Section I, below.

To assist in understanding the terminology and abbreviations used in the medical and scientific journals and by the experts, Appendix A to this opinion contains a glossary. A table of contents for the opinion is located in Appendix B.

Section I. Omnibus Proceedings in Vaccine Act Cases.

A. Historical Use of Omnibus Proceedings under the Vaccine Act.

The Vaccine Act contains no provision for class action suits or omnibus proceedings.[7] However, the Act does permit the consideration of evidence without

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[5] At one time the Petitioners' Steering Committee ["PSC"] advanced three theories of causation, but subsequently reduced that to two, after determining that the evidence in support of the third theory, that the measles component of the MMR vaccine causes some ASDs, was encompassed in the evidence adduced in the Theory 1 cases. Decisions on the second theory, that TCVs alone cause some ASDs, are pending before this court.

[6] *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).

[7] Omnibus proceedings bear some resemblance to multi-district litigation in federal district courts. *See* 28 U.S.C § 1407.

regard to formal rules of evidence. § 12(d)(2)(B). Certain provisions of the Vaccine Act and its legislative history strongly 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 then apply this expertise to the resolution of other cases.[8] Vaccine Rule 8(a) provides: "The special master, based on the specific circumstances of each case, shall determine the format for taking evidence and hearing argument." *See Lampe v. Sec'y, HHS*, 219 F.3d 1357, 1362 (Fed. Cir. 2000), *quoting Hodges v. Sec'y, HHS*, 9 F.3d 958, 961 (Fed. Cir. 1993). The Court of Federal Claims has noted that "instead of being passive recipients of information, such as jurors, special masters are given an active role in determining the facts relevant to Vaccine Act petitions," and that "the special masters have the expertise and experience to know the type of information that is most probative of a claim." *Doe v. Sec'y, HHS*, 76 Fed. Cl. 328, 338-39 (2007). The Federal Circuit has commented on the "virtually unlimited" scope of the special master's authority to inquire into matters relevant to causation (*Whitecotton v. Sec'y, HHS*, 81 F.3d 1099, 1108 (Fed. Cir. 1996)), and the deference properly accorded to their fact-finding (*Munn v. Sec'y, HHS*, 970 F.2d 863, 871 (Fed. Cir. 1992). *See also* J. Weinstein, *Improving Expert Testimony*, 20 U. RICH. L. REV. 473, 494-95 (1985-1986) (encouraging judges presiding over non-jury trials "to become familiar with the scientific background by reading about the issues and discussing them with the experts" and noting that "[t]he court owes an obligation to the parties, to society, and to itself to assist in obtaining the best possible answers to the scientific questions before it.").

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,

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[8] *See, e.g.*, H.R. Conf. Rep. 101-386, 1989 WL 168141 (Novembr 21, 1989) (Conference Report on the 1989 amendments stated that "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."). With special masters experienced in Vaccine Act litigation, medical acronyms, for example, need not be explained anew to a special master who has heard such acronyms in numerous cases. Basic scientific evidence is often cursorily addressed by the experts, with the expectation that the special master will ask questions concerning any matters not completely clear. However, special masters are not doctors; thus they do not "diagnose" petitioners. 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 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 explicating 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).

based on a ruling in an omnibus test case.[9]

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 in 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*, 2002 U.S. Claims LEXIS 371, *62-66 (Fed. Cl. Spec. Mstr. Dec. 15, 2002).

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. The parties are thus 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.

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[9] 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.

Both methods have proven efficient in resolving similar cases by settlement or dismissal, based on the special master's analysis of the scientific evidence. However, the second method has the disadvantage that the special master's findings amount to an advisory opinion. Using the second 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. The Omnibus Autism Proceeding.

1. Creation of the OAP.

On July 3, 2002, Chief Special Master Golkiewicz issued Autism General Order #1 ["Autism Gen. Order # 1"] to address issues arising from the unprecedented filing of more than 300 petitions for compensation in a six-month period, all alleging that vaccines caused a neurodevelopmental disorder known as autism or an ASD.[10] Autism Gen. Order # 1 established the OAP to process efficiently and expeditiously the current ASD petitions as well as the large number of anticipated petitions presenting the same claims.[11]

Autism Gen. Order #1 and the OAP grew out of meetings with an informal advisory committee comprised of members of the petitioners' bar, and legal and medical representatives of the respondent in Vaccine Act cases, the Secretary of Health and Human Services. Autism Gen. Order #1 noted that the large number of petitions already filed, and the even larger number of anticipated petitions,[12] would stretch both the court's resources and those of the bar. Petitioners acknowledged that their cases were not yet ready for adjudication, as they were seeking discovery and additional time for the completion of scientific studies to bolster their claims. Conducting such discovery in the context of an omnibus proceeding, rather than in individual cases, was clearly a more efficient use of resources of both the bar and the court.

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[10] Autism and ASD are discussed in some depth in Section IV.

[11] The publicly accessible website contains the OAP master file, which includes orders, decisions, and periodic updates issued by the special masters assigned to the autism docket. Most of petitioners' and respondent's filings are posted on this website. Beginning in June 2007, audio files and transcripts of the hearings were also posted on this website. The text of Autism Gen. Order #1 may be found at 2002 U.S. Claims LEXIS 365 at *1 (Fed. Cl. Spec. Mstr. July 3, 2002); *see also* http://www.uscfc.uscourts.gov/node/2718 (last visited November 17, 2008).

[12] Over 5100 such petitions have been filed, approximately 4700 of which remain pending before the court. *See* Autism Updates, January 19 and March 14, 2007, *available at* http://www.uscfc.uscourts.gov/node/2718 (last visited on January 31, 2009). Since the OAP was established, over 375 petitions have been resolved by decisions, voluntary dismissals, or involuntary dismissals of petitions filed outside the statute of limitations.

Autism Gen. Order # 1 established the PSC to represent the interests of petitioners. Membership on the PSC was determined by the petitioners' bar, with two attorneys selected by the committee to serve as "lead counsel." The PSC has represented the general interests of autism petitioners continuously since the inception of the OAP. However, counsel of record retained responsibility for all other aspects of their own individual cases, including keeping clients informed about the process, and obtaining medical records and other pertinent documents.[13]

Those petitioners with ASD petitions pending in the Program at the time Autism Gen. Order # 1 was issued were permitted to "opt in" to the OAP, while retaining the right to "opt out" at any time and return their cases to active status for resolution on an individual basis.[14] Relatively few petitioners have availed themselves of this opportunity to opt out of the OAP.

New petitions filed after the issuance of Gen. Order #1 were authorized to use a "Short Form" petition format set forth in the order.[15] *See* Order dated July 8, 2002. By filing such a petition, the filer averred that: (1) the vaccinee suffered from an ASD, or autism-like disorder, that had persisted for longer than six months; (2) the petition was filed within three years of onset of that disorder; and (3) a vaccine listed on the Vaccine Injury Table[16] was the cause of the condition. Chief Special Master Golkiewicz acknowledged respondent's concerns that the short form petitions would not permit evaluation of cases for the statutorily-required documentation,[17] but indicated that the OAP procedures represented the most efficient method for handling the overwhelming

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[13] A few law firms represent substantial numbers of OAP petitioners, with three firms each representing more than 400 petitioners. Other attorneys represent only a few petitioners or even a single petitioner.

[14] Colten's case is somewhat unusual, in that it did not become a part of the OAP until February 13, 2004. At the time his case was transferred to the OAP, medical records, test results, and a number of expert reports were already filed. As a result, some subsequent filings duplicated prior filings and some lacked exhibit numbers. Prior to the hearing in this case, I ordered each party to correct exhibit numbers and to file an updated index of their exhibits each time a new exhibit was filed. *See* Orders, dated August 30 and September 26, 2007 (adopting the new exhibit numbers). Those indices reflect the exhibit numbers referred to throughout this opinion.

[15] In the Vaccine Rule 4 reports filed in response to short form petitions, respondent continued to object to the short form procedure.

[16] 42 C.F.R. § 100.3.

[17] Section 300aa–11(c) of the Vaccine Act requires the petition to be accompanied by certain documentary evidence, including records pertaining to the vaccination and subsequent treatment. *See also* Vaccine Rule 2(e), RCFC, Appendix B.

number of cases.[18]

2. The OAP Discovery Process.

All cases in the OAP were assigned to Special Master George Hastings, who managed the discovery process and other matters arising as the cases moved toward the goal of a hearing on the general causation issue. Based on a draft proposed by petitioners' representatives, Autism Gen. Order # 1 established a master schedule for resolving the ASD cases. The schedule included a discovery period, followed by a hearing on the general issue of causation, within two years of the OAP's inception.

For a variety of reasons, delays ensued. Although the master schedule anticipated completion of discovery and designation of petitioners' experts by August 2003, followed by petitioners' experts' reports in November, 2003, those deadlines were subsumed by disputes arising in the discovery process. As Special Master Hastings noted in January, 2004:

> It is, of course, unfortunate that these discovery disputes are delaying the progress of the Omnibus Autism Proceeding toward an eventual hearing concerning the petitioners' causation claims. However, it is the strategic decision of the Committee [the PSC] to pursue further discovery before presenting the petitioners' causation case. While I am eager to proceed to the presentation of the petitioners' causation case, I will leave this strategic decision to the Committee. If the Committee believes that it will be of advantage to the autism petitioners that the Committee pursue additional discovery before presenting that case, I will defer to the Committee. My role, instead, will be to assist in facilitating the discovery process in any way that I can, and to be ready to promptly hear and rule upon the petitioners' causation case as soon as the petitioners are ready to present it.

Autism Update and Order, January 12, 2004.

Most of the discovery issues were amicably resolved, but some remained contentious. Special Master Hastings issued rulings on several issues that could not be

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[18] The PSC, counsel for respondent, and the OSM have developed and implemented a plan to supplement the short form petitions and to resolve expeditiously those cases with jurisdictional or other defects. Approximately 200 cases per month are added to the process, which entails the filing of sufficient medical records to make a determination whether the case was timely filed and whether the vaccinee has an ASD or similar condition. Further filings then ensue in those cases filed within the statute of limitations and properly assigned to the OAP. Once all the statutorily-mandated documents are filed, the remaining Theory 1 cases will be resolved, at least in part, by the causation evidence filed in the *Cedillo, Hazlehurst*, and *Snyder* Theory 1 test cases and the decisions of the special masters in these three cases. Of course, in accordance with Autism Gen. Order # 1, petitioners may withdraw from the OAP at any time.

resolved by the parties. *See, e.g.*, Autism Update and Order, dated September 24, 2003.

3. Preparations for Hearing the Theory 1 Test Cases.

Autism General Order #1 was written in contemplation of a "general causation hearing" in March, 2004. At the request of the petitioners, this hearing date was postponed. In a lengthy Autism Update and Order issued on August 11, 2005, Special Master Hastings summarized reasons for the delay in the original timetable and addressed a government argument that he lacked the authority to delay the proceedings longer than 420 days. Although he declined to force petitioners to try their cases before they were ready to do so, he set a January 31, 2006 deadline for identification of expert witnesses. After requesting and receiving an enlargement of this deadline, petitioners filed a list of 16 experts on February 14, 2006 and filed a *curriculum vitae* ["CV"] for each of those experts on March 22, 2006. On April 21, 2006, Special Master Hastings deferred the filing of expert reports until December 31, 2006.

On July 18, 2006, the PSC filed a proposal for conduct of the general causation proceedings. The PSC proposed a new hearing date in June, 2007, with the hearing conducted over a two-to-three week period in which petitioners would present evidence regarding all theories of causation. The PSC opposed consideration of any specific case.[19] In September, 2006, Special Master Hastings adopted the PSC proposal for a three-week general causation hearing. He ordered petitioners to file expert reports by February 16, 2007,[20] with respondent's expert reports to be filed 60 days later.[21] At this point, it was still unclear whether the general causation issues would be considered alone, or in the context of a test case.

The plan to consider all theories of causation at a single hearing was later modified. As early as May, 2006, it appeared that the petitioners might request to bifurcate the general causation issue into two separate proceedings, one addressing whether TCVs could cause autism and the other addressing whether the MMR vaccine could cause autism. *See* Autism Update, May 16, 2006. On January 9, 2007, the PSC proposed hearing a single actual case to test the theory that a combination of the MMR vaccine and TCVs caused ASDs. Subsequent hearings to address two other theories,

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[19] One might fairly read Autism Gen. Order #1 as written in contemplation of the second method of conducting an omnibus proceeding, one similar to that used in the rubella arthropathy cases.

[20] They were actually filed on February 20, 2007, after yet another request for delay.

[21] The many delays requested by petitioners to file their expert reports resulted in a highly compressed schedule in the final four months before the *Cedillo* hearing began. Until the petitioners' expert reports were filed on February 16, 2007, respondent did not know precisely what their theory (or theories) of MMR-TCV causation entailed. Thus, respondent's experts had a very tight time schedule in which to review petitioners' expert reports and the scientific and technical literature upon which they were based, and to prepare their own reports and supporting materials.

one in which TCVs alone were causal (Theory 2), and the other in which the MMR vaccine was causal (Theory 3) were planned. The PSC later determined that hearing test cases involving Theory 3 would not be necessary because the evidence pertaining to this theory had been presented during the Theory 1 cases. *See* PSC Notice Re: Theory 3, dated August 7, 2008 and Autism Update, dated September 29, 2008.

The January 9, 2007, PSC filing also addressed an informal proposal by the court that involved detailing two additional special masters to hear the general causation question. The PSC opposed the proposal. Nevertheless, on January 11, 2007, Chief Special Master Golkiewicz assigned two additional special masters to the OAP docket. Special Master Campbell-Smith and I were the two additional special masters assigned. *See* Notice Regarding Assignment of Autism Cases to Additional Special Masters, dated January 11, 2007 (setting forth in some detail the reasons for detailing two additional special masters), filed into the OAP Master File.

Recognizing that special masters have authority to issue causation decisions only in the context of an individual claim for compensation under the Program and that appellate review could ensue only when an individual claim for compensation was decided, the three special masters ordered the PSC to identify three test cases, rather than just one, on each of the theories of causation. After some initial delays, the three test cases on the first theory of causation were identified.[22] Special Master George Hastings was already assigned to the first case identified, *Cedillo*. Special Master Patricia Campbell-Smith was reassigned to the second case, *Hazlehurst*, identified on May 31, 2007. This case, *Snyder*, was not designated as the last of the three cases on Theory 1 until Friday, June 8, 2007, just three days before the June 11, 2007, general causation hearing began in *Cedillo.* It was reassigned to me on June 11, 2007.

The delays in designation of the second and third test cases (*Hazlehurst* and *Snyder*) meant that evidence pertaining to their specific facts could not be presented at the scheduled hearing beginning on June 11, 2007. Practical considerations, including difficulties in rescheduling the nearly twenty identified expert witnesses and in obtaining a courtroom large enough to accommodate the expected public interest[23] in the

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[22] The three special masters issued joint orders permitting the designation of the test cases in the second two theories of causation to be delayed until after the hearings in the first three cases. *See* Autism Update, dated July 12, 2007, at 5-6. Hearings on the Theory 2 test cases took place in May and July, 2008.

[23] The Vaccine Act prohibits disclosure of information submitted to a special master to anyone who is not a party to the proceeding without the express written consent of the person who submitted that information. § 300aa–12(d)(4)(A). Thus, Vaccine Act hearings are not routinely opened to the public. Given the intense public interest in the autism cases and the probable applicability of the testimony in the Theory 1 OAP cases to thousands of other claims pending in the Program, petitioners waived the protection of the statute and asked that the hearing be opened to the public. After expressing initial concerns and opposition, respondent agreed to have the testimony (but not the entirety of the expert reports) publicly disclosed and withdrew objections to opening the *Cedillo* hearing to the public.

hearing, effectively precluded granting an additional delay so that all three cases could be heard together.

The evidentiary procedures adopted in the OAP, and specifically for the Theory 1 test cases, were the subject of considerable discussion during periodic status conferences. Counsel for the PSC and the individual petitioners agreed that all of the evidence developed in these three test cases could be applied to all three cases.[24] Respondent interposed some objections not relevant to this particular case. *See* Snyder Transcript ["Tr."] at 1030-31, 1033-34.

C. Evidence Constituting the Record as a Whole.

The evidence before me thus includes all of the evidence, less the medical records of the other children, introduced before, during, and after the hearings in *Cedillo* and *Hazlehurst*, as well as all of the evidence filed in this case. By Order, dated February 9, 2009, I filed compact disks containing the evidence in *Cedillo* and *Hazlehurst* into the record of this case as Snyder Court Exhibits ["Ct. Ex."] I and II, respectively. In my prehearing order, I indicated my intent to consider, absent any objections, "all evidence, to include expert reports, medical articles, and trial exhibits previously filed in the *Cedillo* and *Hazlehurst* cases, as well as in the OAP master file." Pretrial Order, ¶ 2f, dated September 19, 2007. No objections were filed by either party.[25]

Many exhibits, particularly the medical and scientific journal articles, filed in this case were also filed in *Cedillo* or *Hazlehurst*. Such exhibits were often discussed in the transcript or expert reports by the exhibit number used in that case. To avoid confusion, I will ordinarily identify the exhibit by the designation used in the transcript or report, clearly identifying the case name involved. For example, "Cedillo Pet. Ex. 61, Tab D" or "Hazlehurst Res. Ex. B."

Additionally, the parties agreed to posting audio transcripts of the hearing testimony on the OSM website, to similar posting of the daily transcripts, and to "listen only" telephonic access to the hearing itself. Similar procedures were adopted in the *Hazlehurst* and *Snyder* hearings, with the exception of telephonic access. Hundreds of individuals dialed in to the *Cedillo* hearing; determining how many have accessed (or will access) the audio files or typed transcripts of the hearing is not possible.

[24] No specific agreement governs to what extent evidence adduced in the test cases can be used in resolving the approximately 4800 other cases, but, generally speaking, evidence developed in an omnibus hearing can, at the request of a party, be applied to subsequent cases.

[25] During the *Snyder* hearing, respondent's counsel initially lodged an objection to my consideration of Dr. Kennedy's testimony in the *Snyder* case on the issue of general causation, but immediately acknowledged he was in error. He then affirmed that I could consider all of the testimony in *Cedillo* and *Hazlehurst*. Snyder Tr. at 299A-300A.

Many medical or scientific journal articles were filed as attachments[26] or tabs to expert reports; often, more than one expert attached the same article, resulting in multiple exhibit numbers or letters for the same document.[27] In this decision, the article is primarily identified by one of the several exhibit designations. When two experts discussed the same article in testimony or expert reports, and it is necessary to refer to their individual interpretations of the article, only one exhibit designation is used. For example, a medical journal article might be identified as "Cedillo Res. Ex. D, Tab 36," even if it was also filed as a petitioner's exhibit in this case.[28]

At each hearing, some expert witnesses used slide presentations to aid the court in following key points of their testimony. Other documents were used in cross-examination or in rebuttal testimony. These exhibits were designated as trial exhibits, using the case name, the party offering the exhibit, the term "trial exhibit" and consecutive exhibit numbers. For example, a trial exhibit from the *Cedillo* case might be designated as Cedillo Petitioners' Trial Exhibit 3 ["Cedillo Pet. Tr. Ex. 3"]. A respondent's exhibit from the *Snyder* case might be designated Snyder Respondent's Trial Exhibit 6 ["Snyder Res. Tr. Ex. 6"].

In discussing the evidence in this case, references to testimony are identified with the name of the case in which the testimony was given, the abbreviation "Tr." and the page numbers of the transcript on which the testimony appears.[29]

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[26] Respondent's expert reports identified most of the journal articles as "attachments," rather than "tabs," but the experts were not entirely consistent in this practice. For simplicity, throughout this opinion, any "tab" or "attachment" to an expert report is referred to as "Tab," followed by the letter (petitioners) or number (respondent) assigned to it.

[27] The special masters assigned to the autism cases recognized the potential for confusion caused by multiple exhibit numbers for the same document. In the Theory 2 test cases, we ordered each party to produce a "Master List" of scientific and medical journal articles and similar documents. Even under this system, a document filed by both parties has two different exhibit designations.

[28] The fact that a particular medical journal article was filed by a particular party or by both parties does not constitute a party's endorsement of the article's premise or conclusions. Our practice is to require that a copy of any articles discussed (favorably or unfavorably) in an expert's report be filed with the report. A special master is not required to accept an expert report at face value (*see* § 300aa-13(b)(1) (indicating that "any such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court.")) and may thus explore the basis for the expert's conclusions by reading and evaluating materials cited in the report. *See also Perreira v. Sec'y, HHS*, 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) and *Burns v. Sec'y, HHS*, 3 F.3d 415, 417 (Fed. Cir. 1993).

[29] Accuracy problems with the original transcripts filed in each of the three cases resulted in numerous changes. Revisions were proposed by the parties and the agreed-upon changes were ordered by the special master assigned to that case. In an effort to avoid completely renumbering a transcript already referenced in post hearing briefs, pages with changes were designated by a letter "A" appearing after the page number. If transcript corrections resulted in an additional page, the original page number appears, followed by the letter "B."

The evidentiary record[30] in this case thus encompasses, *inter alia*, nearly four weeks of testimony, including that offered in the *Cedillo* and *Hazlehurst* cases; over 900 medical and scientific journal articles; 50 expert reports (including several reports of witnesses who did not testify);[31] supplemental expert reports filed by both parties post-hearing, the testimony of fact witnesses on behalf of Colten, and Colten's medical records.

In addition to presiding over and hearing all of the testimony in Colten's own case, I was present for all of the testimony in the *Cedillo* case and all of the expert testimony in the *Hazlehurst* case. Thus, my opinions on the credibility of the witnesses are based, in part, on my personal observations of witness demeanor.

D. Expert Witnesses and Their Qualifications.

The expert witnesses included, *inter alia*, neurologists, virologists, toxicologists, immunologists, and gastroenterologists. Speaking generally, the qualifications of the experts proffered by respondent, the relationship of those qualifications to the subject matter of their testimony, and the quality of their testimony far exceeded those of petitioners' experts. For purposes of comparison of qualifications, I have grouped the experts by their primary field of expertise; however, some experts offered opinions in more than one scientific discipline. For example, Dr. Kennedy offered opinions in virology, immunology, and polymerase chain reaction ["PCR"] testing[32]; Dr. Rima offered opinions in virology and PCR testing.

Respondent's experts were practicing physicians and research scientists who have taught and written extensively on the subject matter about which they testified. Only two of petitioners' expert physicians were engaged in clinical medicine. Although most of petitioners' experts had adequate, and occasionally excellent, qualifications as physicians and scientists, they were either not engaged in research, or engaged in research that was, at best, tangential to the subject matter of their testimony. Two of petitioners' witnesses appeared to derive substantial income from expert witness fees.

My evaluation of the quality of the testimony and the qualifications of the witnesses offering that testimony is based, in part, on the factors the Supreme Court set

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[30] The Vaccine Act requires the special master to consider the record as a whole. *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).

[31] Six expert reports prepared by Dr. Jeffrey Bradstreet were filed as exhibits in this case (Snyder Pet. Exs. 1, 17, 18, 21, 26, and 28) prior to the case's transfer to the OAP. Although Dr. Bradstreet testified at the hearing, his testimony was designated as that of a fact witness, as one of Colten's treating physicians. Pet. Prehearing Memo at 4.

[32] *See* Section VI.G.3 for an explanation of PCR testing.

forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 578 (1993) and *Kumho Tire Company, Ltd., v. Carmichael,* 526 U.S. 137 (1999).[33] It is also based on my personal observations of each witness who testified. I emphasize that my decision is not based solely on the experts' relative qualifications; although that is an important factor, it is not, standing alone, determinative. A qualified expert with lesser qualifications may offer an opinion that, for a variety of reasons, is more persuasive than that of a more qualified expert testifying on behalf of an opposing party.

In evaluating matters contained in expert reports filed by witnesses who did not testify, I have considered the experts' qualifications, as reflected in all of their filed curricula vitae ["CV"], the extent to which the experts' opinions were supported by other evidence or testimony, the bases for their opinions, and the nature of their opinions offered in determining how much weight to accord the proffered opinions. I have also considered that the witness was not available for cross-examination or to answer questions posed by me or another of the special masters, recognizing that there is no right of cross-examination in Vaccine Act cases. 42 U.S.C. § 300aa-12(d)(2)(D).

1. Virologists, Vaccines, and Infectious Disease Experts.

Four of the expert witnesses testified primarily about measles virology, vaccines, and diseases. Doctor (Ph.D.) Ronald Kennedy testified for petitioners, and Dr. Diane Griffin, Dr. (Ph.D.) Burt Rima, and Dr. Brian Ward for respondent. It is particularly significant that no measles virologist testified on behalf of petitioners, in view of the fact that petitioners' theory focused on the detection of measles virus and on the purported action of the measles virus on the central nervous and gastrointestinal symptoms.

a. Doctor (Ph.D.) Ronald Kennedy.

Petitioners' primary expert on measles virology was Dr. Ronald Kennedy.[34] Undoubtedly, Dr. Kennedy is a learned and highly qualified virologist, with a specific

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[33] In his opening statement in *Snyder*, petitioners' counsel appeared to agree that *Daubert's* non-exhaustive list of factors to consider in determining the admissibility of an expert's opinion were appropriate factors to consider in weighing and evaluating evidence in this case. Snyder Tr. at 20-21, 27-28, and 33-34.

[34] Doctor Kennedy's expert reports were filed as Cedillo Pet. Exs. 110 and 112 and Snyder Pet. Ex. 30. His CV was filed as Cedillo Pet. Ex. 111. The slides he used to illustrate his trial testimony were filed as Cedillo Pet. Tr. Ex. 8 and Snyder Pet. Tr. Ex. 4. Doctor Kennedy has a doctorate in microbiology with a specialty in immunology from the University of Hawaii. He performed postdoctoral work at the Baylor College of Medicine in the Department of Virology and Epidemiology, with a focus on vaccine development. He currently serves as professor and chair of the Department of Microbiology and Immunology at the Texas Tech University Health Sciences Center. He sits on review panels for the National Institutes of Health, the Department of Defense, and the National Science Foundation. Cedillo Tr. 684-86. He has published over 240 peer reviewed articles, including articles on the topics of viral persistence, vaccines, and HIV. Cedillo Tr. at 686-89.

expertise in vaccines and HIV. However, his qualifications to opine on measles virus and measles vaccine paled in comparison with those of Drs. Griffin, Ward, and Rima.

Most of Dr. Kennedy's experimental work has involved primates, not human beings. Cedillo Tr. at 684-85. His work on vaccines early in his career primarily involved the hepatitis B vaccine and virus. His later work concerned the development of HIV-related vaccines. His current research involves vaccines for types of cancer that are caused by persistent viruses. Cedillo Tr. at 687-88. Doctor Kennedy's one peer reviewed publication[35] on the measles vaccine was a literature survey, coauthored with another of petitioners' expert witnesses, Dr. Vera Byers, when both of them were claimants' experts in the United Kingdom ["U.K."] MMR litigation.[36] He has no current research focus on the measles virus in humans. Cedillo Tr. at 756. *See Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1993) (noting that one factor bearing on admissibility of scientific testimony is whether opinions were developed expressly for purposes of testifying or grew naturally out of research independent of litigation).

I found Dr. Kennedy to be a knowledgeable and engaging witness, albeit one who tended to offer opinions outside his areas of expertise. However, in view of respondent's experts' greater expertise in measles virology, I tended to credit their testimony when the specific issue concerned the measles virus. Although Dr. Kennedy was qualified to testify about PCR testing and technology, I found the testimony of Drs. Bustin and Rima generally more credible, based both on their expertise and demeanor. When the matter in controversy concerned the operations of Unigenetics laboratory, both Drs. Bustin and Rima had considerably more first-hand knowledge than did Dr. Kennedy.

b. Doctor Diane Griffin.

Doctor Griffin was clearly the most highly qualified witness on measles virology.[37] She began studying the measles virus in 1973 or 1974, building on a study of viral

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[35] *See* Cedillo Res. Tr. Ex. 3.

[36] *See* Part E, below. Claims similar to those of petitioners in the OAP involving MMR vaccine and ASD were also the subject of litigation in the U.K.

[37] Doctor Griffin's expert report was filed as Cedillo Res. Ex. V. Her CV was filed as Cedillo Res. Ex. W. The slides she used to illustrate her trial testimony were Cedillo Res. Tr. Ex. 23. Doctor Griffin received her M.D. from Stanford University. She also received a Ph.D. in immunology from Stanford. Cedillo Tr. at 2739A. She did a post-doctoral fellowship at Johns Hopkins and then joined the faculty there with a joint appointment in the Department of Medicine and the Department of Neurology. In 1994, she became the Chair of the Department of Molecular Microbiology and Immunology in the School of Public Health at Johns Hopkins. She has served as an officer and member of a number of professional societies related to medicine and infectious diseases. Cedillo Tr. at 2740-42A. She has edited professional journals and serves on the editorial boards of several others. Cedillo Tr. at 2742A-43A.

encephalitis in general, and post-measles encephalitis in particular, and progressed from the study of that disease into the study of measles vaccine. Cedillo Tr. at 2744-46. She has authored or coauthored around 100 peer reviewed articles and book chapters on the measles virus or measles vaccine. She authored the chapter on the measles virus that appears in FIELDS VIROLOGY, the premier publication used by virologists.[38] Cedillo Tr. at 2746-47. She is currently working on a publication on current topics in measles microbiology and immunology, along with Dr. Michael Oldstone, another widely recognized expert in virology and in the study of measles. Cedillo Tr. at 2747-48.

Doctor Griffin's testimony was a model for expert witnesses, in spite of, or perhaps because of, her inexperience in testifying. She provided careful, reasoned, and responsive answers, and appropriately qualified her opinions. Her testimony was highly compelling and completely convincing.

c. Doctor Brian Ward.

Doctor Ward began his study of measles during his training in infectious diseases at Johns Hopkins, where he spent two years at Dr. Griffin's laboratory and in field research in Peru, studying the measles virus.[39] Cedillo Tr. at 1796A-97. In the course of his career, Dr. Ward has seen hundreds of cases of measles virus infection. Snyder Tr. 940. His laboratory was extensively involved in efforts to isolate measles virus genomic material from human tissue, giving him an expertise in PCR technology and testing as well. Cedillo Tr. at 1848-53A.

I found Dr. Ward to be an eminently qualified expert witness, who offered clear, concise, and highly probative testimony.

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[38] D. Griffin, Chapter 44, *Measles Virus*, found in D. Knipe and P. Howley (Eds.), FIELDS VIROLOGY, Vol 1: 1401-41, Lippincott Williams & Wilkins, Philadelphia (2001), filed as Cedillo Res. Ex. R, Tab 18. A 1996 version of this chapter was filed as Cedillo Pet. Ex. 61, Tab DD. During the *Snyder* hearing, it was clear that Dr. Kennedy's testimony and expert report drew heavily on Dr. Griffin's measles chapter in the 1996 version of this book. *See* Snyder Tr. at 1000-04A.

[39] His expert reports were filed as Cedillo Res. Ex. BB and Snyder Res. Exs. K, M, and O. His CV was filed as Cedillo Res. Exs. I and C and Snyder Res. Ex. L. The slides he used to illustrate his testimony were filed as Cedillo Res. Tr. Ex. 12. Doctor Ward graduated from medical school in Canada, completed a residency in internal medicine and infectious diseases at Johns Hopkins, and a Canadian residency in microbiology. He is board certified in internal medicine and infectious diseases in the United States and in internal medicine and infectiology in Quebec. After serving as the chief of the Infectious Disease department at McGill University, he returned to research in the Division of Infectious Diseases there. He also teaches at the graduate and undergraduate level. Snyder Tr. at 940; Cedillo Tr. at 1796A-98A. He has published articles and book chapters on virology, infectious diseases and vaccines. Snyder Tr. at 940. The current focus of his research is on viruses and intracellular parasites, including malaria and leishmania, and immune response to those infections. Cedillo Tr. at 1798A. He testified as an expert witness on three prior occasions, one involving civil litigation, one involving Quebec's version of the Vaccine Program, and in one Vaccine Act case. Cedillo Tr. at 1798A-99.

d. Doctor (Ph.D.) Bertus Rima.

Doctor Rima's primary focus in research over the last 33 years has been the paramyxoviruses and, in particular, the measles virus.[40] After working on cloning and sequencing the measles virus, he is now focused primarily on the pathogenesis of the virus. His list of publications includes more than 100 articles on the measles virus and approximately 20 book chapters (including those on mumps). He has lectured on measles as an invited speaker, and has been a part of several World Health Organization ["WHO"] groups evaluating measles vaccines and vaccination programs. Snyder Tr. at 826A-27A.

For a period of about five years, Dr. Rima was one of the defense experts in the U.K. MMR litigation. His report was filed in two parts, with the first a general description of measles virus and virology, and the second an evaluation of the claims for the presence of measles virus in the tissue of various claimants in the litigation. His work also involved explaining measles virology to the legal teams. His appearance in the *Snyder* hearing was the first time he had testified in court. Snyder Tr. at 828A-830A.

Doctor Rima was a superb expert witness. He was well-qualified in the subject matter of his testimony, testified directly and forthrightly, and made extremely difficult topics understandable. He made his disapproval of certain laboratory practices perfectly plain, without engaging in *ad hominem* attacks.

2. Neurologists and Psychiatrists.

All of the experts who testified about matters pertaining to neurology were well-qualified in terms of academic qualifications, professional certifications, training, and general experience. However, in terms of experience in the pathogenesis, diagnosis, and treatment of autism, respondent's experts had greater qualifications. In contrast to petitioners' experts, Drs. Kinsbourne and Corbier, respondent's experts, Drs. Fombonne, Rust, Wiznitzer, and Cook, had far more experience in treating children with ASD and much more extensive research experience in and publications concerning ASD.

a. Doctor Marcel Kinsbourne.

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[40] Doctor Rima's expert reports were filed as Snyder Res. Exs. S and V. His CV appears at Snyder Res. Ex. W. He has a Ph.D. in bacterial genetics and did his post-doctoral work on the measles virus. He is currently the head of the school of Biomedical Sciences at Queens University, Belfast. In addition to his administrative responsibilities, he teaches at the undergraduate through postgraduate levels. He peer reviews scientific journal articles (approximately 50 per year) and is on the editorial board of several scientific journals. He has reviewed grant proposals in the past, but is not currently sitting on any grant panels. Snyder Tr. at 824A-28. His research has also included work on canine distemper and mumps virus.

Doctor Marcel Kinsbourne is a highly qualified pediatric neurologist, although he is board certified only in pediatrics, having begun practice as a pediatric neurologist before it was recognized as a subspecialty.[41] Cedillo Tr. at 1037A-38. He has written chapters for medical textbooks, including one on disorders of mental development in a prominent textbook on child neurology. He has published over 400 articles on a variety of subjects, including five or six on various aspects of autism. He has conducted no research into autism's causes or treatment. He has not seen, diagnosed, or treated a child with autism for more than 17 years.

He served as one of the claimants' expert witnesses in the U.K. MMR-autism litigation for about four years, reviewing expert reports, scientific articles, medical records, and making numerous trips to London to meet with other experts. Cedillo Tr. at 1102-07.

Doctor Kinsbourne was the pivotal petitioners' witness on causation in both *Cedillo* and *Snyder*, providing the theories upon which the causation cases were based. In some measure, his testimony that measles virus caused some cases of autism reflected one of the concerns about expert testimony reliability discussed in *Kumho Tire*. In what has become known as "the same intellectual rigor" test, the Supreme Court stated that a 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. In a book chapter he authored, filed as Cedillo Pet. Ex. 61, Tab PP,[42] Dr. Kinsbourne included a chart on the causes of autism. In his testimony in *Cedillo*, he used the same chart, but with one addition; he included measles as a cause. Cedillo Tr. at 1169-70. A fair assessment of this change is that Dr. Kinsbourne was unwilling to say measles was a cause of autism in a publication for

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[41] Doctor Kinsbourne's expert reports were filed as Cedillo Pet. Ex. 61 and Snyder Pet. Exs. 29 and 215. His CV was filed as Cedillo Pet. Ex. 62. He received his medical degree from Oxford University Medical School and did 11 years of post-graduate training in pediatrics and neurology. He began teaching at Oxford University in experimental psychology, and subsequently taught pediatric neurology at Duke University Medical Center, where he also served as chief of the division of pediatric neurology. After seven years at Duke, he moved to the University of Toronto, where he served as a professor of Pediatrics for six years. He turned then to full-time research at the Eunice Kennedy Shriver Center, where he served as chief of the Division of Behavioral Neurology and where he obtained numerous grants from NIH and other agencies. His work there focused on children with attention deficit hyperactivity disorder and similar conditions. Cedillo Tr. at 1028A-30A. He significantly reduced his clinical practice in 1991 and since then has seen patients only occasionally. He was the first to describe an immune-mediated neurological disorder sometimes called Kinsbourne Syndrome. Since 1995, he has been a professor of psychology at the New School University in New York, where he teaches graduate students. Cedillo Tr. at 1030A-32A. He is a member of numerous societies and was the president of the International Neuropsychological Society and the Society for Philosophy and Psychology. He served as policy advisor to the NIH's Institute for Communication Disorders. Cedillo Tr. at 1038-40.

[42] M. Kinsbourne and F. Wood, Chapter 18*, Disorders of Mental Development*, pp. 1097-1156, found in J. Menkes, *et al.*, eds., CHILD NEUROLOGY, 7th Ed. (Lippincott, Williams, and Wilkins: Philadelphia) (2006).

his peers, but was willing to do so in a Vaccine Act proceeding.

Another concern is that Dr. Kinsbourne suffers from the stigma attached to a professional witness–one who derives considerable income from testifying in Vaccine Act cases. In the 20 years of the Vaccine Program's existence, Dr. Kinsbourne has appeared as an expert witness in at least 185 decisions.[43] This figure does not include his opinions in the many unpublished cases adopting stipulations of settlement, nor does it reflect pending cases in which he has filed an expert opinion. Payment for expert testimony is expected, and the mere receipt of payment does not, of itself, cast doubt upon an expert's qualifications or opinions. *See Daubert*, 43 F.3d at 1317 (noting, however, that an expert's normal workplace should be "the lab or the field, not the courtroom or lawyer's office"). I emphasize that I gave Dr. Kinsbourne's opinions full and fair consideration, and that the frequency in which he appears as a petitioners' witness was but one small factor in the myriad of reasons I found them to be unpersuasive.

b. Doctor Jean Ronel-Corbier.

Doctor Corbier is a board certified neurologist with a specialty in child neurology.[44] He is currently practicing as a clinical neurologist in Concord, NC, where he treats children with neurological problems, including autism. Hazlehurst Tr. at 266A. His focus is on clinical practice rather than research. He has no publications in the scientific literature about ASD, although he has written and self-published several books dealing with ASD.

Doctor Corbier presented as an earnest and sincere witness, albeit one whose expert opinions were heavily laced with generalities, speculation, and conjecture. He cited journal articles as supporting his opinions when they clearly did not. He holds sincere beliefs concerning the role of vaccines in triggering or causing regressive autism, but his beliefs were largely unsupported by the evidence.

c. Doctor Eric Fombonne.

Doctor Eric Fombonne testified as an expert witness in the fields of neurology

[43] A LEXIS search in the Court of Federal Claims database conducted on December 19, 2008, disclosed 215 cases in which the name Kinsbourne appeared, either as an expert witness or as having filed an expert report. Removing duplicates (cases appealed or those involving both a causation decision and a fees and costs decision), approximately 185 cases remain.

[44] Doctor Corbier's expert report was filed as Hazlehurst Pet. Ex. 26. His CV is at Hazlehurst Pet. Ex. 27. He is a board certified neurologist with a special qualification in child neurology. Hazlehurst Tr. at 266A.

and epidemiology.[45] He is a professor of psychiatry at McGill University in Montreal, Canada, where he heads the Division of Child and Adolescent Psychiatry. Cedillo Tr. at 1239. He also heads the Autism Spectrum Program at Montreal Children's Hospital, the pediatric hospital of McGill University. Cedillo Tr. at 1248A. For the last 22 years, Dr. Fombonne has worked extensively in the area of ASD. Cedillo Tr. at 1244A. In addition to his academic work and lecturing about autism, Dr. Fombonne diagnoses and treats children with autism and is currently providing treatment for approximately 200 patients annually. Cedillo Tr. at 1253A-55A.

He previously served as an advisor to the U.K. equivalent of the U.S. Surgeon General concerning the MMR-autism controversy as an expert in both epidemiology and autism. Cedillo Tr. at 1261A-62A. He first began research into the allegation of a link between MMR vaccine and autism in the United Kingdom during 1998, when Dr. Wakefield proposed the link. Cedillo Tr. 1239-40A. He has participated directly in eight to ten epidemiologic studies of autism. He has published over 160 articles related to PDD and childhood behavioral disorders in peer reviewed publications, 34 book chapters pertaining to such disorders, and serves on the editorial board of one journal and has served as a reviewer or a member of the editorial board of several other journals. Cedillo Tr. at 1255A-57. He is a member of the grant review board for "Autism Speaks," which also funds some of his research. Cedillo Tr. at 1429A-31A.

Doctor Fombonne was an excellent witness. He was eminently qualified to offer opinions on both the diagnosis and treatment of autism and on the epidemiologic research into its causes. I note that his testimony about epidemiology was entirely unrebutted.

d. Dr. Edwin H. Cook.

Doctor Cook is board certified in psychiatry and in child and adolescent

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[45] Doctor Fombonne's expert report was filed as Cedillo Res. Ex. P. His CV was filed as Cedillo Res. Exs. C and Q. The slides he used to illustrate his testimony were filed as Cedillo Res. Ex. 8. He graduated from medical school at the University of Paris. He did a residency in psychiatry at the University of Paris with a specialty in child and adolescent psychiatry, with the equivalent of board certification. In addition to his medical degree, he has a master's certificate in biostatistics. He teaches epidemiology methods in child psychiatric research at McGill University. Cedillo Tr. at 1241-42A, 1250A. He also trains autism researchers through a grant program funded by the Canadian equivalent of the NIH. Cedillo Tr. at 1251. In addition to his Master's certificate in epidemiology, he ran a multi-centric randomized clinical trial, trained in a summer program in the United States, and began his own epidemiological research in 1985 into child psychiatric disorders. Cedillo Tr. at 1244A-45A. In 1989, he became a tenured research scientist with the French institute that carries out most of the biomedical research in France, the French equivalent of the NIH. Cedillo Tr. at 1245A-46A. Doctor Fombonne testified that he had occasionally consulted in lawsuits involving alleged links between vaccines and autism on behalf of the pharmaceutical industry. He testified in a *Daubert* hearing in a civil suit against vaccine manufacturers, the only time he appeared as an expert witness prior to the *Cedillo* hearing. Cedillo Tr. 1260A-61A.

psychiatry.[46] He has also served as an examiner for candidates for board certification. He is a professor of psychiatry and the visiting director of autism and genetics at the University of Illinois in Chicago. Since 1984, he has been involved in diagnosing and treating children with autism and continues to see and treat patients with autism two days per week. His current research efforts include the genetics of autism and attention deficit hyperactivity disorder, as well as the pharmacogenetics of cancer. Cedillo Tr. 1468A-72A.

He was recently appointed as a corresponding editor for a new journal on autism research. He is the co-chair of the American Academy of Child and Adolescent Psychiatry's Autism and Intellectual Disability Committee. He was one of the first members of the scientific advisory board of "Cure Autism Now." Cedillo Tr. at 1480A-81A. He has published over 150 peer reviewed articles, including over 30 articles on autism's genetics. Cedillo Tr. at 1481A.

Doctor Cook was an excellent expert witness, and highly qualified to offer opinions about autism's genetics. As he was involved in clinical trials of secretin and research into several other possible therapies, he was well-qualified to offer opinons about the efficacy of various treatments as well. Most of his testimony was entirely unrebutted by petitioners' experts.

e. Dr. Max Wiznitzer.

Doctor Wiznitzer is board certified in pediatrics, pediatric neurology, and in neurodevelopmental disabilities.[47] He completed a two-year fellowship in disorders of

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[46] Doctor Cook's expert report was filed as Cedillo Res. Ex. N. His CVs were filed as Cedillo Res. Exs. B and O. The slides he used to illustrate his testimony were filed as Cedillo Res. Tr. Ex. 10. He received his medical degree from the University of Texas in 1981. He holds the first patent ever granted for a gene-linked drug treatment. Cedillo Tr. at 1467-68A. In addition to teaching and supervising graduate and medical students, he also supervises residents and fellows at the University of Illinois and in several research facilities across the country. Cedillo Tr. at 1470A-71A. His involvement in studies of the genetics of autism includes collaboration with other researchers in Europe and North America and studies conducted in his own laboratory. Cedillo Tr. at 1482. He serves on the editorial board for several professional journals. Cedillo Tr. at 1480.

[47] Doctor Wiznitzer's expert reports were filed as Cedillo Res. Ex. DD and Snyder Res. Exs. Y and DD. His CVs appear as Cedillo Res. Exs. J and EE and Snyder Res. Ex. B . The slides he used to illustrate his testimony are Cedillo Res. Tr. Ex. 11. Doctor Wiznitzer obtained his medical degree from Northwestern University, in Chicago, Illinois, through an honors program. He did a residency in pediatrics, followed by a one-year training program in child developmental disorders, followed by additional specialty training in neurology and child neurology. He is an associate professor of Pediatrics, Neurology and International Health at Case Western Reserve University's School of Medicine. He teaches medical students, supervises interns and residents, and teaches grand rounds. Cedillo Tr. at 1565-71A. He is a member of the editorial board of three medical journals, reviews articles for these and other journals, and is currently involved in writing and reviewing examination questions for board candidates in the developmental behavioral pediatrics examinations. Cedillo Tr. at 1572-75.

higher cognitive function, focusing primarily on language development and autism. He is a staff child neurologist, and formerly the head of the Child Neurology department at Rainbow Babies and Children's Hospital, in Cleveland, Ohio, where he is part of the epilepsy team. He is affiliated with the autism center at the hospital. Cedillo Tr. at 1565-69A.

He has served as the chair of the Child Neurology Society and as the secretary of a group dealing with neurobehavioral disorders, which includes autism. He has been active in several professional groups dealing with the diagnostic criteria for autism and meeting the educational needs of autistic children. He has an active clinical practice treating children with autism and other ASDs, seeing approximately 200-250 patients a month within his own clinic, about 25% of whom have diagnoses on the autism spectrum. He sees additional patients in outreach clinics in Ohio. Cedillo Tr. at 1571-77, 1586. Doctor Wiznitzer is currently researching the pharmacokinetics of drugs in the treatment of children and adolescents with autism. Cedillo Tr. at 1577A-78.

He has testified in other Vaccine Act cases and spends from five to 10 percent of his time doing medical-legal work, most often in the form of reviews of cases. Cedillo Tr. at 1584A-85. He was an expert witness at a *Daubert* hearing in a North Carolina case involving Rhogam and autism in 2006. Cedillo Tr. at 1676-77.

Doctor Wiznitzer was an excellent expert witness, and well-qualified one to offer opinions on autism's diagnosis, cause, and treatment. He was the witness primarily, although not exclusively, involved with rebutting Dr. Kinsbourne's opinions on the biological mechanisms by which vaccine strain measles virus could cause autism. Doctor Wiznitzer's greater qualifications contributed to the greater credibility of his opinions on this topic. His opinions were buttressed by the scientific journals he discussed and cited. I found him forthright and credible.

f. Dr. Robert Rust.

Doctor Rust is board certified in pediatrics and neurology with special qualifications in child neurology.[48] Hazlehurst Tr. at 449A. He is currently a Professor of Epileptology and Neurology at the University of Virginia, where he is also the co-

[48] Doctor Rust's expert opinion was filed as Hazlehurst Res. Ex. E. His CV appears as Hazlehurst Res. Ex. F, and the slides he used to illustrate his testimony were filed as Hazlehurst Res. Tr. Ex. 1. Doctor Rust attended medical school at the University of Virginia where he also did immunological research. He trained in pediatrics, child neurology, and neurochemistry at Washington University in St. Louis, where he also did a fellowship in neonatal neurology. He remained on the faculty at Washington University after completing his fellowship. Hazlehurst Tr. at 448A-49A. He served as the director of the cerebral palsy clinic, and the director of program and training in child neurology at the University of Wisconsin, and directed the training in child neurology at Boston Children's Hospital. Hazlehurst Tr. at 449A. He has served on the editorial boards of and as a reviewer for numerous professional journals. He has published approximately 50 peer reviewed articles and a similar number of book chapters. Hazlehurst Tr. at 450A-511A.

director of the Epilepsy and Child Neurology Clinic and the director of the child neurology training program. Hazlehurst Tr. at 446A, 449A. He recently received an award from the Child Neurology Society, recognizing him as the person who has made the most distinguished contributions to child neurology. He has an active clinical practice where he has treated several hundred patients with autism. Hazlehurst Tr. at 450A-52A.

Doctor Rust was an exceptional witness, testifying clearly and credibly on the topic of autism's pathogenesis. His credibility was enhanced by the fact that he has testified twice before in Vaccine Act cases, both times on behalf of petitioners. Hazlehurst Tr. at 531A.

3. Immunologists.

a. Doctor Vera Byers.

Doctor Byers is board certified in internal medicine. She completed fellowships in protein chemistry and in clinical immunology.[49] She also has a Ph.D. in immunology. Although she described herself as "board eligible" in allergy and immunology, other evidence indicated that this is not a recognized classification.[50] Cedillo Tr. at 863; 956-57. Most recently, she has worked as a consultant for attorneys with clients exposed to toxic chemicals, and as a consultant for biotech companies. Cedillo Tr. at 866-68A. She has no active clinical practice. Although she has written approximately 200 articles, only one of them dealt with measles virus (a literature survey that she coauthored with Dr. Kennedy when they were both claimants' expert witnesses in the U.K. MMR litigation). Cedillo Tr. at 975A-76A. None of her publications concerned mercury. Cedillo Tr. at 975A-76A, 983A.

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[49] Doctor Byers' expert report was filed as Cedillo Pet. Ex. 57. She graduated from the University of California at San Francisco Medical School. Her CV (Cedillo Pet. Ex. 58) described her as a medical toxicologist. The slides used to illustrate her testimony were filed as Cedillo Pet. Tr. Ex. 9. She testified that she held faculty appointments at UCSF in the Department of Medicine and then in the Department of Dermatology. She has done research into tumor immunology and testified that she was one of the founders or initial workers in the field of tumor immunology, was the "world's expert" in poison oak and poison ivy dermatitis, worked in one of the first biotechnology companies, and was on the faculty of the University of Nottingham in England as a senior lecturer from 1984-2000, where she did cancer and monoclonal antibody research. She invented the first monoclonal antibody to be tested in clinical trials and invented the first of the antibodies that led to the use of antibodies to treat leukemia and lymphomas. She started a company that uses biologic-based therapies to treat allergies. She had a clinical practice in allergy and immunology from 1981-2000. She ran the immunology division of the Levin Clinical Labs from 1977-79 and founded the largest AIDS clinic in San Francisco. She is a member of an NIH committee on small business innovative research, holds 10 patents, and formerly served on two editorial review boards for scientific journals. Cedillo Tr. at 863-71A.

[50] She testified that the American Board of Allergy and Immunology recognized and used the term "board eligible." Cedillo Tr. at 957. Cedillo Res. Tr. Ex. 4, reflected that the Board does not recognize, define, or use the term "board eligible."

Doctor Byers' credibility was not enhanced by several instances of apparent "resume padding." Her CV indicated that she was still on the faculty at the University of Nottingham, although her work there ended in 2000. Doctor Byers explained that it was "an old CV." Cedillo Tr. at 960A. Her CV described that she was "Medical director on the team responsible for filing the BLA [Biologics License Application] for Embrel," that secured approval for Embrel as a treatment for rheumatoid arthritis. She acknowledged on cross-examination that this statement was "not exactly correct" and that she was "a consultant medical director." Cedillo Tr. at 958-60A. When informed that there was no record at the FDA of Dr. Byers playing any role in the Embrel licensing application, she stated that the information did not make any difference because she was a member of the team that secured Embrel's approval. Cedillo Tr. at 959-60A. Her testimony on cross-examination regarding her faculty status at UCSF was somewhat confusing. She stated that she was an adjunct faculty member and participated in rounds with the doctors there from 1974-1981and in 1984, and "was there episodically probably through about two years ago." In preparation for her evaluation of the U.K. litigants, she spent three or four months in the immunodeficiency clinic to "find out what was new." Cedillo Tr. at 960A-64A. Her other involvement with the UCSF medical school was using the library, attending social functions, and taking a class in biostatistics. Cedillo Tr. at 964A. According to the university (Cedillo Res. Tr. Ex. 5), she taught an occasional class, but had "no significant activity in the last decade."

Doctor Byers' CV described her as a "medical toxicologist" with "hands-on experience in assessing medical damage to over 3000 patients in the past 15 years." Cedillo Pet. Ex. 58 at 1. Her testimony indicated that these were patients seen to determine if litigation concerning toxic exposures was warranted. She had not seen patients, other than in a litigation context, for the prior seven years. Cedillo Tr. at 964A-966.

Even without considering Dr. Byers' apparent misstatements on her CV, I find that she was not a particularly good expert witness. Her testimony was disjointed and often unclear. It was apparent, particularly when she testified about the purported effects of mercury on the immune system, that she did not have a solid understanding of the toxicokinetics of mercury, and she strayed into matters beyond her expertise. Doctor Byers' insistence that it was acceptable to use adult norms to measure the immune function of infants and young children (Cedillo Tr. at 994) was, frankly, incredible, particularly when she was provided with documents reflecting the relevant pediatric norms.

b. Dr. Christine McCusker.

Doctor McCusker is a pediatric immunologist.[51] She is board certified in pediatrics by the American Board of Pediatrics and holds the equivalent Canadian certification in pediatrics and allergy and immunology. She is now an examiner for the Canadian certification in allergy and clinical immunology. Cedillo Tr. at 2202-03; Hazlehurst Tr. at 560A-61A, 563A-64A. She is the principal investigator of a research laboratory at McGill University, where her research focuses on the development and regulation of the immune system from infancy through adolescence. She is the clinical director of the immunology laboratory at Montreal Children's Hospital. Her professional responsibilities are evenly divided between research and clinical duties. Cedillo Tr. at 2203-05A; Hazlehurst Tr. at 561A-62A.

Doctor McCusker sees approximately 200 pediatric patients per month. This includes a pediatric walk-in clinic, allergy immunology evaluations, and shifts in the emergency room at Montreal Children's Hospital. She is published in the field of pediatric immunology. Cedillo Tr. at 2205A-06; Hazlehurst Tr. at 562A-65A.

I found Dr. McCusker to be a careful and credible witness, one whose opinions were enhanced by clinical experience, work in running a laboratory, and publications in the field of pediatric immunology.

c. Doctor Burton Zweiman.

Doctor Zweiman is board certified in internal medicine and immunology.[52] He is currently an emeritus professor of medicine and neurology at the University of Pennsylvania, School of Medicine. He began his tenure at the University of Pennsylvania in 1963, and, for 24 years, served as the chief of the Division of Allergy and Clinical Immunology. Snyder Tr. at 570A.

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[51] Doctor McCusker's expert reports were filed as Cedillo Res. Ex. Z and Hazlehurst Res. Ex. C. Her CVs were filed as Cedillo Res. Ex. AA and Hazlehurst Res. Ex. D. The slides used to illustrate her testimony were filed as Cedillo Res. Tr. Ex. 16. She holds a Ph.D. in immunogenetics and a medical degree, both from McMaster University. She did a residency in pediatrics, a fellowship in allergy and clinical immunology, and a post-doctoral fellowship in immunology. She is an Assistant Professor at McGill University, teaching undergraduates, medical students, graduate students, and residents courses in immunology. She has testified twice as an expert witness in cases other than the OAP. She has been a reviewer for several professional journals. Cedillo Tr. at 2202-06; Hazlehurst Tr. at 562A-65A.

[52] Doctor Zweiman's expert report was filed as Snyder Res. Exs. C, F, J, and N, and his CV was filed as Snyder Res. Ex. D. The slides supporting his testimony were filed as Snyder Res. Tr. Ex. 2. He received his medical degree from the University of Pennsylvania. Following his residency, he took a fellowship in allergy and clinical immunology. Although he recently stopped treating patients, he still consults with his colleagues about patient diagnosis. Snyder Tr. at 570A. He is a member of a number of immunologically-related professional organizations, and has received a number of honors and awards for distinguished service and teaching. Snyder Tr. at 571A.

In the laboratory he founded and helped supervise for many years, he conducted research related to autoantibodies and neuroimmunology. Snyder Tr. at 570A. In addition to his past service on the editorial boards of several immunology journals, his resume lists more than 200 publications. Snyder Res. Ex. D, pp. 5-23.

Doctor Zweiman was a well-qualified expert witness. His opinions were supported by the scientific and medical literature. I found him to be both knowledgeable and forthright, and far more qualified than Dr. Bradstreet to opine on the significance of Colten's immune system testing and treatments.

d. Doctor Robert Fujinami.

Although respondent filed an expert report and CV from Dr. Fujinami in the *Cedillo* case, he was not called to testify.[53] His qualifications to opine on immunology are quite impressive. I relied on his report primarily for background information on immunology not supplied by Dr. Byers.

e. Doctor Andrew Zimmerman.

Although respondent filed an expert opinion and CV from Dr. Zimmerman in the *Cedillo* case, he was not called to testify during the hearing.[54] However, his qualifications to testify as a pediatric neurologist, with a special interest in behavioral neurology and autism, were excellent. Some of the research he conducted or in which he participated was the subject of considerable testimony, particularly that concerning the significance of immune system pathology in brain biopsies of those with ASD. I relied on his report in considering the relative merits of various interpretations of his research findings.

4. Gastroenterologists and Gastrointestinal Specialists.

a. Dr. Arthur Krigsman.

Doctor Krigsman was called not only as an expert witness[55], he was also a

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[53] Doctor Fujinami's expert report was filed as Cedillo Res. Ex. R. His CV was filed as Cedillo Res. Exs. D and S.

[54] Doctor Zimmerman's expert report was filed as Cedillo Res. Ex. T, and his CV was filed as Snyder Res. Ex. U. The slides supporting his testimony were filed as Snyder Res. Tr. Ex. 3.

[55] Doctor Krigsman's expert report was filed as Cedillo Pet. Ex. 59, and his CV was filed as Cedillo Pet. Ex. 60. The slides he used to explain his testimony were filed as Cedillo Pet. Tr. Exs. 2 and 3. Doctor Krigsman received his medical degree from the State University of New York. He completed a three-year pediatric residency, and a three-year fellowship in pediatric gastroenterology. Cedillo Tr. at 409. From 1995 until 2000, he served as the Director of the Department of Pediatric Gastroenterology at

treating doctor for Michelle Cedillo.[56] He is board certified in pediatrics and pediatric gastroenterology, and is currently in private practice as a pediatric gastroenterologist. Cedillo Tr. at 409. He no longer practices general pediatrics. Cedillo Tr. at 507. He began treating children with autism and bowel disorders in 2000. Cedillo Tr. at 411-19.

Other than his board certification, Dr. Krigsman's credentials were scanty and his professional record reflected a 2005 fine imposed by the Texas State Board of Medical Examiners for an advertisement that he was available to see patients at a time before he was licensed to practice medicine in Texas. Cedillo Tr. at 501-02. While he was an attending physician at Lenox Hill Hospital in New York from 2000-2004, the hospital became concerned that he was performing medical procedures on autistic children for research purposes, rather than for medical necessity. He sued the hospital for what he viewed as a restriction on his privileges. Cedillo Tr. at 499A-500, 558-60. He testified that the pathology findings supported his decision to perform the colonoscopies. Cedillo Tr. at 559A-62.

He served as an expert witness for the claimants in the U.K. MMR litigation. He did not know if he performed endoscopies on any of the children who were claimants in that litigation. Cedillo Tr. at 506-07.

He is currently the director of gastroenterology services at Thoughtful House Center for Children in Austin, Texas, along with Dr. Andrew Wakefield, a key figure in the genesis of the MMR-autism hypothesis. Cedillo Res. Tr. Ex. 1; Cedillo Tr. at 492A.

Although his CV stated that he is a clinical assistant professor at New York University, Dr. Krigsman never taught a class at or received a salary from the university. Cedillo Tr. at 503-04. Of the four listed publications on his CV, one was never published. Another was a slide presentation he made at an autism research meeting. A third listed publication was actually a poster and abstract of preliminary data presented at an autism research meeting, leaving him with one published article. Cedillo Tr. at 504-06.

Although qualified to testify about pediatric gastroenterology, Dr. Krigsman's testimony about autistic enterocolitis as a diagnostic entity was speculative and unsupported by the weight of the evidence.

Beth Israel Hospital in New York. He then joined Lenox Hill Hospital in a similar capacity. Cedillo Tr. at 410-11.

[56] He diagnosed Michelle Cedillo with inflammatory bowel disease before he ever examined her, based on the medical records and reports from her mother. Cedillo Tr. at 512A-15. Although he testified that, based on the results of the endoscopies, she had nonspecific enterocolitis, not Crohn's disease, in November, 2003, he wrote a letter that indicated she had Crohn's disease. Cedillo Tr. at 518-20. Although there is no record that he ever saw Colten Snyder, he ordered tests and prescribed medication for him, as reflected in Snyder Pet. Ex. 12, pp. 238-43, 305 (Dr. Bradstreet's medical records).

b. Doctor (Ph.D.) Thomas MacDonald.

Doctor MacDonald is a professor of immunology and the dean for research at Barts and the London School of Medicine and Dentistry.[57] In addition to his Ph.D., he conducted postdoctoral research into how gut microbes influence T cell function. He has been a researcher in the field of immunology since 1973. Hazlehurst Tr. at 603-605A. His current research field is the human gastrointestinal system, particularly that of children, with a focus on inflammatory bowel disease. He runs a laboratory where he does research on inflammation in the human gastrointestinal tract. Hazlehurst Tr. at 606A.

He has published over 150 peer reviewed articles in the field of gastrointestinal immunology and has recently published a book on the same subject. He edited seven or eight books on gut immunology and wrote hundreds of book chapters. He served on the editorial board of the journal *Gut* for seven years, and on the editorial board of *Gastroenterology* for six years. He is an associate editor of the journal *Inflammatory Bowel Diseases*. He also reviews articles for *Gut, Science, Nature, Lancet*, and other highly rated scientific journals. He is the only gut immunologist elected as a Fellow of the U.K.'s Academy of Medical Science. Doctor MacDonald delivers frequent lectures on gut immunology, gut inflammation, and inflammatory bowel disease. Hazlehurst Tr. at 607A-11A.

Although he is not a medical doctor, I found Dr. MacDonald eminently qualified to testify on diseases and immunology of the digestive system. He was an exceptionally candid witness, with the academic and research credentials and the experience to support fully his candid testimony.

[57] Doctor MacDonald's expert report was filed as Hazlehurst Res. Ex. A, and his CV was filed as Hazlehurst Res. Ex. B. He received his Ph.D. in immunology from the University of Glasgow. He conducted two years of postdoctoral work in immunology at the Trudeau Institute in Saranac Lake, New York. The slides used to illustrate his testimony were filed as Hazlehurst Res. Tr. Ex. 2. His current position involves administering the research at the London School of Medicine and Dentistry, with six institutes and 300 researchers. He is in charge of all the immunology instruction at the school and personally teaches about inflammatory bowel disease and gastroenterology. He teaches undergraduates, graduates students, medical students, and postgraduate researchers. He sits on a panel for the Medical Research Council of the U.K., which is the equivalent of the NIH. At one point in his career, he worked for Merck. He currently works closely with the pharmaceutical industry to develop new therapies for the treatment of inflammatory bowel disease. He was an expert in the U.K. MMR litigation, evaluating evidence about the presence of measles virus in the guts of autistic children and whether autistic enterocolitis actually exists. His appearance in the *Hazlehurst* case was his first appearance as an expert witness. Hazlehurst Tr. at 604A-07A, 610A-12A, 666-67A.

c. Dr. Stephen B. Hanauer.

Doctor Hanauer is board certified in internal medicine and gastroenterology.[58] He is a professor of medicine in Clinical Pharmacology and chief of the section of Gastroenterology, Hepatology, and Nutrition at the University of Chicago. His fellowship involved specialty training in digestive diseases and he spent several months training in pediatric gastroenterology. Cedillo Tr. at 2077A-78A. His special teaching focus is inflammatory bowel disease. He is a frequent lecturer on inflammatory bowel disease at other universities and for professional groups or organizations. Cedillo Tr. at 2079A-80.

He has received awards for clinical research and clinical care from the American Gastroenterological Association. He was the chair of the Crohn's and Colitis Foundation's Clinical Alliance, a group of institutions collaborating in research related to Crohn's disease and ulcerative colitis, and he currently serves on the committee dedicated to research initiatives, looking for novel projects involving the cause of or treatment for ulcerative colitis or Crohn's disease. He serves on the board of trustees of the American College of Gastroenterology and has chaired the International Organization of Inflammatory Bowl disease. Cedillo Tr. at 2078A-80.

In addition to his academic and other professional responsibilities, Dr. Hanauer maintains an active clinical practice, focusing on clinical research into the epidemiology and potential causes of ulcerative colitis and Crohn's disease, and therapies for both conditions. Much of this research is funded by pharmaceutical companies. Cedillo Tr. at 2084-86.

He has published over 280 peer reviewed articles related to gastrointestinal issues, including inflammatory bowel disease, and over 70 book chapters. He serves on the editorial boards of nine medical journals, and is the editor-in-chief of a newsletter related to recent advances in inflammatory bowel disease, ulcerative colitis, and Crohn's disease. Cedillo Tr. at 2083-84.

Although, unlike Dr. Krigsman, Dr. Hanauer is not a board certified pediatric gastroenterologist, the lack of this certification did not impact on his credibility. His

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[58] Doctor Hanauer's expert report was filed as Cedillo Res. Ex. X, and his CV was filed as Cedillo Res. Exs. G and Y. His slides used to support his testimony were filed as Cedillo Res. Tr. Ex. 15. He attended the University of Illinois medical school and trained in internal medicine. He completed a two-year fellowship in gastroenterology at the University of Chicago. He remained there after his fellowship. Cedillo Tr. at 2077A-78A. He is the section editor for two journals and is responsible for soliciting and reviewing articles for those journals in his area of expertise. He is a reviewer for many medical journals. Cedillo Tr. at 2083-84. Doctor Hanauer has testified as an expert witness approximately 50 times, primarily in medical malpractice cases, and has appeared for both plaintiffs and defendants. He has testified on a few occasions in toxic tort cases and is currently consulting with Roche Pharmaceuticals on litigation, but none involving vaccines. Cedillo Tr. at 2086.

testimony focused on the distinctions between various forms of gastrointestinal diseases, which are not limited to children, and the pathology and diagnostic criteria for those diseases. I found him to be a well-qualified and highly credible witness. His association with, and research funding by, pharmaceutical companies, which had nothing to do with vaccines or vaccine causation of gastrointestinal disorders, did not appear to pose any conflicts of interest in his testimony.

d. Doctor Michael Gershon.

Although respondent filed an expert report and CV from Dr. Gershon in the *Cedillo* case, he was not called to testify during the hearing.[59] However, his seminal discoveries as the "father of Neurogastroenterology," including understanding "the function and development of the enteric nervous system ("the second brain"), serotonin signaling in the gut, and the rationale for treating gastrointestinal disorders with drugs that affect serotonin signaling in the gut," underscore his impressive qualifications as an expert in gastroenterology and neurobiology. Cedillo Res. Ex. T, p. 3.

5. Toxicologists, Medical Toxicologists, and Immunotoxicologists.

Three witnesses with excellent qualifications testified on the subject of mercury toxicology: Dr. Aposhian for petitioners, and Drs. Brent and McCabe for respondents. Although Dr. Byers offered some testimony on mercury toxicology, she lacked the qualifications to opine credibly on this topic. Doctors, Aposhian, Brent, and McCabe all had impressive qualifications in their fields. In evaluating their testimony, I considered Dr. Brent's greater qualifications as a medical toxicologist. I also found his testimony on mercury's effects much more credible than that of Dr. Aposhian, who, after testifying about the various species of mercury, tended to conflate their effects.

The difference between a toxicologist and a medical toxicologist is significant. Medical toxicologists are medical doctors who must complete a two-year post-residency fellowship in an accredited medical toxicology program and must pass a certifying examination. In contrast, there are no certifications or educational requirements for toxicologists. There are about 250 board certified medical toxicologists in the U.S. Doctor Brent is one of them; Dr. Aposhian is not. Cedillo Tr. at 2310-12. Doctor McCabe, is not a medical toxicologist, but he is an immunotoxicologist, with 20 years of metal immunotoxicology experience and with impeccable qualifications in this field. He testified primarily about the significance of Colten's mercury testing.

a. Doctor (Ph.D.) Vasken Aposhian.

Doctor Aposhian has a Ph.D. in physiological chemistry from the University of

[59] Doctor Gershon's expert report was filed as Cedillo Res. Ex. T, and his CVs were filed as Cedillo Res. Exs. E and U.

Rochester.[60] He conducted postdoctoral work in the Department of Biochemistry at Stanford University School of Medicine and held sabbatical scholar-in-residence positions at MIT and the University of California, San Diego. He is a professor of Molecular and Cellular Biology at the University of Arizona and a professor of Pharmacology at the same university's medical school. Cedillo Tr. at 63. He has conducted research on heavy metals, including mercury, and has a number of publications, including those concerning the effects of mercury on human health. Cedillo Tr. at 65. In his capacity as an environmental toxicologist, he has consulted with other countries and governmental bodies on mercury, including committees from NIH, FDA, and EPA. Cedillo Tr. at 63-64. He was involved with efforts to standardize the recommended limitation on methylmercury among various U.S. government agencies. Cedillo Tr. at 66-69A. He has an impressive list of publications on toxicology, including many on mercury toxicology. Of all petitioners' expert witnesses, Dr. Aposhian had the most impressive qualifications directly pertaining to the subject matter of his testimony.

Doctor Aposhian testified in a reasonably coherent and focused manner on direct examination, when much of his testimony consisted of reading his slides (Cedillo Pet. Tr. Ex.1). However, during cross-examination and questioning by the special masters, Dr. Aposhian's testimony was at times unfocused and sometimes non-responsive. He appeared to lose his train of thought on several occasions and had difficulty understanding questions. Although some of his difficulty may have stemmed from hearing problems, he did not have difficulty in understanding the questions to the same degree during his slide-focused direct examination.

b. Dr. Jeffrey Brent.

After completing medical school, Dr. Brent did a subspecialty fellowship in medical toxicology and thereafter accepted a faculty appointment at the University of Colorado Health Sciences Center.[61] Cedillo Tr. at 2296. He is a full clinical professor at

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[60] Doctor Aposhian's expert report was filed as Cedillo Pet. Ex. 55, and his CV was filed as Cedillo Pet. Ex. 56. The slides used to illustrate his expert testimony were filed as Cedillo Pet. Tr. Ex. 1. Cedillo Tr. at 63. He currently teaches one undergraduate class on exposures to toxic substances in everyday life. He described himself as an environmental toxicologist. Cedillo Tr. at 65-66.

[61] Doctor Brent's expert report was filed as Cedillo Res. Ex. L, and his CVs appear as Cedillo Res. Exs. A and M. The slides that accompanied his testimony were filed as Cedillo Res. Tr. Ex. 17. Doctor Brent obtained a Ph.D. in biochemistry at the Mount Sinai School of Medicine. He did a postdoctoral fellowship at Columbia University College of Physicians and Surgeons. Doctor Brent then attended medical school at the State University of New York's School of Medicine. He performed his internship at Harvard and completed his residency at Emory University School of Medicine. He is a recent recipient of the Louis Roche Award from the European Association of Poison Control Centers and Clinical Toxicologists. Cedillo Tr. at 2297. He does clinical pharmacology and toxicology consultation on adverse effects of drugs or chemicals, which involves teaching toxicology students about patient evaluation, care, and treatment. Cedillo Tr. at 2302-03. In the early 1990s, he lectured once for a pharmaceutical company and had some pharmaceutical company grants during his fellowship years. He has not received any

the University of Colorado Health Sciences Center in Denver. Cedillo Tr. at 2295-96.

Doctor Brent is one of 250 board certified medical toxicologists in the U.S. Cedillo Tr. at 2310-12. He frequently lectures on toxicology, is a member of the American Academy of Clinical Toxicology, and the American College of Medical Toxicology, and several other professional groups. Cedillo Tr. at 2298. He is a senior editor of *Clinical Toxicology* and a peer reviewer for the *New England Journal of Medicine* and the *Journal of the American Medical Association*, and several occupational and environmental medical journals. He has over 200 publications, including peer reviewed articles, book chapters, letters, and abstracts. Cedillo Tr. at 2298-99.

His private practice focuses exclusively on issues related to medical toxicology, primarily involving occupational or environmental exposure to toxins. Cedillo Tr. at 2303-05. He has treated a number of patients with mercury toxicity and has used chelation therapy in patients with toxic mercury exposure. He has also examined or treated children with autism for ingestion of toxic substances and for suspected mercury toxicity. Cedillo Tr. at 2305-08.

Doctor Brent was a well-qualified and credible expert witness.

c. Doctor (Ph.D.) Michael McCabe.

Doctor McCabe received his Ph.D. in microbiology and immunology from Albany Medical College.[62] He is an associate professor in immunology and immunotoxicology in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. Snyder Tr. at 734A. In that capacity, he teaches graduate students in the areas of metal toxicology, immunotoxicology, and autoimmunity. He

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grants from pharmaceutical companies in the last 15 years, but was an investigator on an FDA grant in conjunction with Orphan Medical, a drug company that specialized in the development of niche drugs that larger drug companies would not develop. Cedillo Tr. at 2299-2300, 2384. He has previously testified as an expert witness twice on behalf of a pharmaceutical company, including a recent deposition in a case involving an allegation that thimerosal caused autism. In the early 1990s, he was the chair of a national panel assessing health risks from silicone breast implants, and subsequently testified in a number of cases regarding his work on that issue on behalf of the medical device manufacturers. Cedillo Tr. at 2300-02.

[62] Doctor McCabe's expert report was filed as Snyder Res. Ex. T, and his CV was filed as Snyder Res. Ex. U. The slides supporting his testimony were filed as Snyder Res. Tr. Ex. 3. He began his work in immunotoxicology in graduate school, in the Department of Microbiology and Immunology, at Albany Medical College. Snyder Tr. at 737A. He had two-years of postdoctoral training at the Karolinska Institute, in Sweden. Following this, he returned to the United States as a faculty member at the Institute of Chemical Toxicology in Detroit, Michigan. Snyder Tr. at 735A-36. His laboratory is currently researching how lymphocyte activation is modulated by metal exposure. Snyder Tr. at 741-42. He has received a number of awards including the Young Outstanding Immunotoxicologist Award from the Immunotoxicology Specialty Section of the Society of Toxicology in 2000. Snyder Tr. at 746.

also runs a laboratory that conducts research into metal immunotoxicology. Snyder Tr. at 740-41.

Doctor McCabe sits on the editorial boards of several of the leading professional journals in the fields of toxicology and immunotoxicology. He has published around 40 papers on immunotoxicology or related topics. Snyder Tr. at 744-47.

Although his field of expertise is somewhat esoteric, Dr. McCabe's testimony was not. He testified clearly and credibly about Colten's mercury exposure and the significance of the various types of tests ordered by Dr. Bradstreet.

6. PCR Experts.

a. Doctor (Ph.D.) Karin Hepner.

Doctor Hepner's doctorate from UCLA is in molecular biology.[63] She has worked in the field of PCR technology and techniques since 1994. Cedillo Tr. at 583A-84A. At the time of her testimony, she had authored or coauthored four papers, none of which dealt with the detection of measles virus through PCR. Cedillo Tr. at 636-37.

Her testimony was primarily an explanation of PCR testing, but she also provided an evaluation of a paper describing the PCR techniques employed by Unigenetics laboratory. I found her to be a credible and conscientious witness, but her experience in PCR was considerably less than that of Dr. Rima or Dr. Bustin. Where their opinions, particularly on Unigenetics' operations as described in a peer reviewed paper, diverged, I generally accepted the testimony of the more experienced witnesses.

b. Doctor (Ph.D.) Steven Bustin.

Doctor Bustin has a Ph.D. in molecular genetics from Trinity College, Dublin, Ireland.[64] He conducted his postdoctoral research on positive strand-RNA viruses. He is a senior research fellow at London Hospital Medical College, and is currently the chair of Molecular Science at Queen Mary's Medical School at the University of London. Cedillo Tr. at 1933-34.

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[63] Doctor Hepner's report was filed as Cedillo Pet. Ex. 63, and her supplemental report as Cedillo Pet. Ex. 120. Her CV appears as Cedillo Pet. Ex. 64. The slides used to illustrate her testimony were filed as Cedillo Pet. Tr. Ex. 7.

[64] Doctor Bustin's expert report was filed as Cedillo Res. Ex. UU. His two reports in the U.K. MMR litigation were filed as Cedillo Res. Exs. XX and WW and Snyder Res. Exs. Q and R. His slides were filed as Cedillo Res. Tr. Ex. 13. Other than his involvement in the U.K. MMR litigation (addressed, *infra)*, Dr. Bustin has never offered an opinion in a legal proceeding. The *Cedillo* case was the first time he ever testified in court. Cedillo Tr. at 1962A-64A.

Over the course of his career, he developed an expertise in PCR techniques, and currently uses PCR in his research. His laboratory was one of the first academic labs in the U.K. to use TaqMan PCR. Doctor Bustin's laboratory has published 14 peer reviewed articles in journals and eight or nine book chapters on PCR in the last five years. One of the articles on quantitative real-time PCR has been cited in peer reviewed literature more than 1,000 times; a follow-up paper has been cited over 500 times. In 2004, Dr. Bustin wrote and edited one of the definitive books on quantitative PCR. Cedillo Tr. at 1934A-36A.

He is a fellow of the Royal Society of Medicine, reviews papers for scientific journals, has organized three national meetings on PCR, and travels worldwide giving lectures on PCR. Cedillo Tr. at 1936A-37A.

Doctor Bustin was one of the most highly qualified and credible expert witnesses I have ever encountered.

7. Treating Physician: Dr. J. Jeffrey Bradstreet.

Although Dr. Bradstreet was identified as a treating physician rather than as an expert witness for the hearing, he filed six expert reports before Colten's case became part of the OAP.[65] Additionally, his publications were discussed and critiqued during the course of the trial. Prior to beginning his testimony, he corrected a mistake in one of his publications which had listed him as an adjunct professor at Stetson University. Although he believed he was so appointed, at the time of the article's publication, he subsequently learned that the appointment was not properly processed. Snyder Tr. at 140-42.

Doctor Bradstreet is licensed to practice medicine in Florida and Arizona. Snyder Tr. at 140. He is a family physician who has chosen to limit his practice to children with ASD and ADHD. He is not board certified in any medical specialty (Snyder Tr. at 143A, 261A), although he was one of the experts in the U.K. MMR litigation. *See* Cedillo Res. Tr. Ex. 6 (document reflecting payments to expert witnesses in the U.K. MMR litigation). Doctor Bradstreet thus presented as a blend between treating physician and expert. As the reports he filed as an expert were not withdrawn as exhibits, it is appropriate to consider his qualifications to opine on the cause of Colten's condition. His credentials are less robust than most expert witnesses, even those who testify under the relaxed evidentiary requirements in Vaccine Act cases. I note that two courts have refused, based on *Daubert*, to permit him to testify as an expert witness in cases alleging that vaccines cause or contribute to ASD. *See Redfoot v. B.F. Ascher & Co.*, 2007 U.S. Dist. LEXIS 40002, *38-40 (N.D. CA 2007) (although a

[65] Doctor Bradstreet's expert reports are filed as Snyder Pet. Exs. 1, 17, 18, 21, 26, and 28, and his original CV is filed as Snyder Pet. Ex. 16. A later (corrected) CV was filed as Snyder Pet. Tr. Ex. 1. The slides he used to support his testimony were filed as Snyder Pet. Tr. Ex. 2.

treating doctor, Dr. Bradstreet's testimony on matters related to TCVs and autism was excluded as to matters about which he was not a percipient witness), and *Easter v. Aventis Pasteur, Inc.*, 358 F.Supp.2d 574 (E.D. TX 2005) (Dr. Bradstreet found not qualified to opine on vaccine causation).

Nevertheless, I considered Dr. Bradstreet's six reports and the medical journal articles he authored, in addition to his medical records and testimony pertaining to Colten in rendering my opinion on the specific causation claim in Colten's case.

E. U.K. MMR Litigation.

Claims similar to those of petitioners in the OAP involving the MMR vaccine and ASD were also the subject of litigation in the U.K. The litigation against the manufacturers of the MMR vaccine was largely concluded, without resolution of the issues presented, when public funding for the claimants was withdrawn. *See Sayers v. SmithKline Beecham*, 2004 WL1640222 (Queen's Bench 2004). Before the conclusion of the publicly-funded litigation, numerous expert reports and studies were filed. Respondent obtained access to some of these materials through an application to the U.K. court, and filed them as exhibits into the three test cases.

Petitioners in the *Cedillo* and *Hazlehurst* cases filed motions to strike these exhibits; petitioners in *Snyder* did not. Although the *Snyder* case does not directly present the same challenge to the introduction of materials and evidence obtained from the U.K. MMR litigation presented in the *Cedillo* and *Hazlehurst* cases, the PSC obliquely raised objections to consideration of such evidence in *Snyder* on two occasions. The first instance was during a recorded status conference on June 8, 2007, before the designation of *Snyder* as a test case, when the PSC attorney objected to the consideration, in any of the test cases, of any expert reports from the U.K. litigation, unless all of the expert reports from that litigation were made available to petitioners. Cedillo Status Conference Transcript ["Cedillo SC Tr."] at 40. The second was in a document filed in the Autism Master File and in the *Snyder* case on July 31, 2008. *See* PSC Notice Re: UK Litigation Materials and the First Theory of General Causation (filed simultaneously in *Cedillo, Hazlehurst* and *Snyder*) at 3 (noting "objections to the admission of evidence from the U.K. as was introduced during these hearings"). To place this issue into perspective, some background is necessary.

On February 14, 2006, the PSC filed Petitioners' Initial Disclosure of Experts, designating 16 expert witnesses. *See* Docket of Omnibus Autism Proceeding ["OAP Master File"] (available at http://www.uscfc.uscourts.gov/node/2718) (last visited Nov. 24, 2008). After one enlargement of time, on June 15, 2006, respondent filed a list containing the names of three experts and a request for leave to designate additional experts, noting that petitioners' theory of causation was still being developed and that, without a hearing date, respondent could not obtain the commitment of some experts to participate. *See* Notice of Expert Witnesses, dated June 15, 2006, OAP Master File.

Pursuant to matters discussed during a February 9, 2007 OAP status conference, the three special masters granted the PSC (and counsel for petitioners in the *Cedillo* case) additional time to file expert reports, setting a deadline of February 20, 2007. Respondent's deadline for filing expert reports was similarly extended until April 24, 2007. *See* Order Granting Time Extension, filed February 13, 2007, OAP Master File.

Petitioners in *Cedillo* timely filed four expert reports covering general and specific causation issues on Theory 1 on February 20, 2007. After receipt of these expert reports, respondent's litigation team began identifying and interviewing potential expert witnesses. By mid-March, it became apparent that the laboratory results from Unigenetics were a key feature in petitioners' case.[66] Cedillo SC Tr. at 13-15. Unigenetics' results were similarly important in the U.K. MMR litigation, and in April, 2007, respondent's counsel contacted the Office of Foreign Litigation within the Department of Justice to begin efforts to obtain materials filed in the U.K. MMR litigation. Recent statutory changes in the U.K. to enable third parties to obtain civil litigation materials had never been litigated, and, therefore, efforts to obtain these U.K. litigation materials were subject to considerable scrutiny. Cedillo SC Tr. at 13-15.

On March 23, 2007, respondent identified eleven experts who would address general causation issues during the *Cedillo* case.[67]

On May 11, 2007, Special Master Hastings ordered the parties to file all documentary evidence, including medical literature, by May 25, 2007. On May 22, 2007, petitioners filed the additional expert medical report (in letter format) of Dr. Karin Hepner,[68] without requesting leave of court to file an additional expert report after their February 20, 2007, deadline. Petitioners also filed additional medical literature and the

[66] Unigenetics' testing program is discussed at length in Section VII; the laboratory result in question was a report from Unigenetics documenting the presence of measles virus genomic material in specimens of tissue taken from Michelle Cedillo. Colten Snyder's case also involved similar laboratory reports, which are discussed in Section VIII.

[67] This document was filed in *Cedillo*, No. 98-816V, but not in the OAP Master File. All of the remainder of the filings discussed in this section were also made in the *Cedillo* case, unless the text and citations indicate otherwise.

[68] Doctor Hepner's expert report largely concerned the reliability of test results for measles virus, including those of Michelle Cedillo, that were performed by Unigenetics laboratory. Samples of Colten's blood, gut tissue, and cerebrospinal fluid ["CSF"] were also tested at Unigenetics. These tests are discussed in Section VIII, below.

expert report of Dr. Ronald Kennedy[69] out of time on May 28, 2007.[70]

Respondent filed affidavits of Drs. Steven Bustin and Bertus Rima on May 22, 2007, as part of a motion to exclude evidence from Unigenetics' testing. On May 31, 2007, respondent filed the expert report of Dr. Bustin (Cedillo Res. Ex. UU), which directly addressed issues raised in Dr. Hepner's letter.

On June 7, 2007, respondent filed a number of documents obtained from the U.K. MMR litigation, including two reports by Dr. Steven Bustin. At a June 8, 2007 status conference, petitioners objected to the court's consideration of these materials, and lodged similar objections to the anticipated filing of additional reports by Drs. Peter Simmonds and Bertus Rima. Respondent indicated that the latter two reports from the U.K. were expected within hours. Cedillo SC Tr. at 11-12.

Respondent also provided background information concerning how these materials had been obtained and what occasioned their late filing. Cedillo SC Tr. at 10-13. A review of the materials already in the public domain reflected that several of petitioners' experts in *Cedillo* had also served as experts in the U.K. litigation. In early May, 2007, respondent decided to attempt to obtain their reports and some evidence pertaining to Unigenetics' testing from the U.K. court. The initial application to release certain documents was filed on May 18, 2007 before Justice Keith, with a request for an expedited hearing.[71] Justice Keith heard the application on May 24, 2007. He expressed some concerns about the lack of notice to the U.K. claimants, as well as to the breadth of the materials being requested. He set another hearing for June 5, 2007. Cedillo SC Tr. at 15, 17-19.

Based on Justice Keith's comments at the May 24th hearing, respondent narrowed his request for documents, removing from the original application the request for the reports from petitioners' experts[72] in *Cedillo* and those of several other witnesses. The revised application focused specifically on matters pertaining to Unigenetics laboratory and the laboratory's testing procedures. Respondent's counsel

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[69] Doctor Kennedy's report concerned the measles virus and measles vaccine, but also commented on the reliability of Unigenetics' measles virus testing program.

[70] A signed copy of this report, along with accompanying medical literature, was filed as Cedillo Pet. Ex. 112 on June 1, 2007.

[71] A copy of that application was filed in *Cedillo* on June 8, 2007, as Attachment 2 to respondent's Notice of Filing. Respondent did not assign it an exhibit number.

[72] The original application to the U.K. court sought release of the reports filed by Drs. Kinsbourne, Krigsman, Byers, Wakefield, and Bradstreet (*see* Cedillo SC Tr. at 31), three of whom were witnesses in *Cedillo* (Drs. Kinsbourne, Krigsman, and Byers) and two of whom were witnesses in *Snyder* (Drs. Kinsbourne and Bradstreet). The amended application was filed by respondent as Attachment 3 to respondent's June 8, 2007 Notice of Filing in *Cedillo*.

noted that attempts to obtain the remaining tissue from Michelle Cedillo's gut biopsy for testing were unsuccessful because Unigenetics laboratory no longer existed. Cedillo SC Tr. at 19.

Justice Keith considered the revised application in a June 5, 2007 hearing, and, on June 6, ruled that four expert reports could be released, subject to redaction of any personal claimant information.[73] By the time of the *Cedillo* and OAP status conference on June 8, 2007, two reports were redacted, released to the respondent's counsel, reviewed by them, and filed as exhibits. A third report was redacted and released to respondent's counsel, and was awaiting review. The fourth report was still partially in transit between the U.K. and respondent's counsel. Cedillo SC Tr. at 20-22.

During the June 8, 2007 status conference, petitioners argued that none of the reports should be considered as evidence because they were untimely. Counsel noted that the hearing in *Cedillo* was scheduled to begin in three days, on June 11, 2007. Petitioners also noted that they had sought release of U.K. litigation material through third party subpoenas to Merck three years earlier,[74] and that it appeared respondent had obtained information from the pharmaceutical industry, putting petitioners at a disadvantage. Based on late filing and unfair prejudice, they asked that the information obtained from the U.K. court be excluded.

Apparently ignoring the fact that the U.K. court controlled release of the U.K. litigation materials, petitioners renewed a request for the court to subpoena Merck and other manufacturers to obtain the reports of all 65 experts in the U.K. litigation. Petitioners contended that respondent's application to the U.K. court was a "sovereign to sovereign" request that received extraordinary treatment. Finally, petitioners objected to the court's consideration of any reports if their authors would not be made available for cross-examination. Cedillo SC Tr. at 23-27. Petitioners conceded that they knew about attempts to obtain documents from the U.K. litigation more than two

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[73] Justice Keith's Order was filed as Attachment 4 to respondent's June 8, 2007, Notice of Filing in *Cedillo.*

[74] *See* OAP Master File, July 16, 2004, Ruling Concerning Motion for Discovery from Merck RE: MMR Vaccine, in which Special Master Hastings denied the PSC's request for these materials. Given the U.K. court's protective order on witnesses, it does not appear that Merck could have released those materials without the consent of the U.K. court, even if ordered to do so by Special Master Hastings. The PSC counsel conceded as much when he noted that their experts who were also experts in the U.K. litigation were subject to protective orders and, therefore, could not discuss their knowledge of the U.K. proceedings. Cedillo SC Tr. at 36. However, nothing barred those experts from indicating that the U.K. litigation files contained material that might be relevant to the OAP litigation. Respondent also noted that Dr. Bustin's reports were not filed with the U.K. court until after the PSC's request for third party discovery from Merck. Cedillo SC Tr. at 43.

weeks prior to this status conference.[75] Cedillo SC Tr. at 28.

Special Master Hastings considered petitioners' objections to fall into two categories: (1) late notice and filing, making preparation to counter the reports at the hearing difficult, and (2) the limited nature of the reports produced. With regard to late notice, he commented that petitioners filed a number of documents (including one expert report) after the May 25th deadline. Cedillo SC Tr. at 45-46. With regard to "cherry picking" only four reports, he proposed that the special masters join respondent and petitioners in a joint application to the U.K. court for disclosure of all additional reports sought by either side. Cedillo SC Tr. at 47-49. He also proposed conducting the *Cedillo* and general causation hearings as planned on June 11, 2007, but reconvening at a later time to hear evidence derived from the U.K. expert reports to mitigate the problem with late notice and disclosure. Cedillo SC Tr. at 50-51.

Counsel for the *Cedillo* petitioners continued to object to any consideration of matters derived from the U.K. expert reports at the *Cedillo* trial, but did not oppose having additional proceedings once full access to the U.K. litigation materials was obtained.[76] Cedillo SC Tr. at 53. Counsel for the PSC agreed to request disclosure of the U.K. litigation documents. Cedillo SC Tr. at 52. Respondent's counsel expressed a willingness to join the court in requesting the U.K. litigation materials. Cedillo SC Tr. at 54-55.

Between the *Cedillo* hearing in June, 2007, and the *Snyder* hearing in November, 2007, it is unclear what, if anything, petitioners were doing to obtain the additional U.K. litigation materials. At the *Snyder* hearing, petitioners once again characterized respondent's efforts to obtain material from the U.K. litigation as a "sovereign to sovereign" request. Snyder Tr. at 25, 1013A. Mr. Powers, appearing as both a PSC attorney and as one of Colten's attorneys, argued that petitioners' experts wanted to use information from the U.K. litigation, but could not obtain it. He asserted that witnesses for the plaintiffs in that litigation were "beaten up for three years by the pharmaceutical industry, being prevented from doing their jobs, from treating patients, from running the lab, from publishing research and from teaching because they were barraged with endless interrogatories and requests for documents, endless and endless." Snyder Tr. at 25-26. As no evidence concerning these assertions was filed, it is unclear where Mr. Powers obtained his information.

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[75] Respondent's counsel identified the date of the status conference at which the pending request was discussed as May 23, 2007, and noted that petitioners' counsel merely requested a copy of any document received. Cedillo SC Tr. at 34.

[76] Petitioners in *Cedillo* later filed a motion to exclude the expert report and testimony of Dr. Bustin as duplicative. *See* Motion to Exclude, dated June 18, 2007, filed in *Cedillo*. Petitioners renewed the motion in a much expanded filing made on August 8, 2007. Petitioners later filed supplemental expert reports of Drs. Hepner and Kennedy in the *Cedillo* record to address Dr. Bustin's testimony and his reports from the U.K. litigation. *See* Cedillo Pet. Ex. 120 and 121.

During the testimony of Dr. Kennedy in *Snyder*, petitioners' counsel elicited that Dr. Kennedy was aware of material in the U.K. MMR litigation that would help establish that the laboratory results from Unigenetics pertaining to Colten's CSF were "scientifically credible" but that the information was still under seal by the U.K. court. Snyder Tr. 350A-51A. In response to a question I posed, Dr. Kennedy indicated that he had not been asked to support the release of his own report in the U.K. MMR litigation, and had no objection to its release. Snyder Tr. 424A-25A.

After Dr. Kennedy's testimony, I noted that some five months earlier, the three special masters had invited the petitioners to apply to the U.K. to seek release of whatever matters from the U.K. MMR litigation they desired. In response to my questions, counsel for the PSC (who appeared as co-counsel on behalf of Mr. and Mrs. Snyder and Colten) indicated that "they" (presumably referring to the PSC) had made inquiries, but were informed by outside counsel that they could not obtain the information. He also stated that petitioners' counsel was actively investigating what needed to be done to gain release of documents.[77] I noted that the government obtained release of the four reports requested from the U.K. MMR litigation in a far shorter period than the five months between the June 8, 2007 status conference and the *Snyder* hearing. I urged petitioners to proceed with speed and diligence. Snyder Tr. at 433A-35A. Once again, respondent's counsel noted that they would be supportive of petitioners' efforts to obtain release of additional information from the U.K. litigation. Snyder Tr. at 435A.

During cross-examination of Dr. Rima, petitioners' counsel asked a series of questions concerning proposed retesting of some of the U.K. claimants' samples. Snyder Tr. at 920A-23. During this testimony, Dr. Rima referred to a confidentiality order. Snyder Tr. at 923. It was not entirely clear from his testimony that the confidentiality order to which he referred was from the court, as it appeared that this discussion involved experts working with the attorneys representing the U.K. defendants and, thus, may have involved attorney work-product. At that point, Mr. Powers asked for leave of court to file a supplemental report once the remaining matters from the U.K. litigation were unsealed. I inquired when petitioners expected to make the request to the U.K. court to release additional matters, and Mr. Powers responded that the "process has begun." Snyder Tr. at 923-24. After describing five months of no apparent progress in requesting release, I informed counsel that petitioners needed to move speedily. Snyder Tr. at 924-25.

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[77] Petitioners' counsel's characterization in *Snyder* of the efforts to obtain additional U.K. reports differs from the statement that appears in the notice the PSC filed on July 31, 2008. *See* PSC Notice Re: UK Litigation Materials and the First Theory of General Causation ["PSC Notice Re: UK Litigation"] at 2 ("In the period between the *Cedillo* and *Snyde*r hearings, the petitioners sought, unsuccessfully, to obtain the claimant-side reports from the UK."). This statement implied that petitioners actually made some effort to obtain the U.K. litigation materials. It was apparent to me from Dr. Kennedy's testimony that his support for release of his report had not been sought, and from the on-the-record response of counsel to my questions, that petitioners' efforts to obtain these materials had not progressed to the stage of making any application, or, indeed, anything beyond talking about the process. *See* Snyder Tr. at 924-25.

Later in the hearing, another of petitioners' counsel, Mr. Wickersham, expressed his concern and willingness to do what was necessary to obtain the U.K. expert reports, commenting that his experts were all willing to waive any objections to the release of their reports. He requested that I subpoena the reports from the U.K. court. I noted that the Hague Convention governed subpoenas in foreign jurisdictions, and that a subpoena for a document under seal was not the normal method of obtaining it. Once again, respondent's counsel offered to assist petitioners in obtaining any documents they sought, and stated that U.K. law allowed third parties, including private litigants, to obtain matters filed under seal. Snyder Tr. at 1011A-13A.

Between November, 2007, and July, 2008, the special masters repeatedly raised the issue of petitioners' attempts to obtain additional evidence from the U.K. MMR litigation at our periodic status conferences with the parties. At no point did the PSC indicate that an application had actually been made. All three special masters signed a letter indicating our support for release of the documents sought by petitioners.[78] Several of the experts who prepared reports for the U.K. court agreed to the release of their work. Others, including Drs. Orla Sheils and John O'Leary, were apparently unwilling, as they reportedly did not respond to efforts to contact them. Ultimately, based on the delay and expense that would be involved in litigating the release of some reports without the consent of the experts, the PSC chose not to seek the release of any of the additional expert reports. *See* PSC Notice Re: UK Litigation at 2.

It may well be true that the petitioners' efforts to obtain additional material from the U.K. MMR litigation would have been entirely unsuccessful. However, based on the precedent established by Justice Keith's release of four expert reports, it appears that, at a minimum, petitioners could have obtained the reports of their own experts and those of any of the respondent's experts. Because the application to the U.K. court was never made, we simply do not know what the court would have done.

Petitioners attempted on several occasions to shift the responsibility for requesting such evidence from their shoulders to the court's. In each case, the court declined to shoulder petitioners' burden, while, nevertheless, supporting petitioners' efforts by conveying the court's desire that the evidence be released.

I note that petitioners failed to lodge any specific objection in *Snyder* to my consideration of the expert reports of Dr. Bustin, in contrast to the motions to strike his expert reports, testimony, and trial presentation filed in *Cedillo* and *Hazlehurst*. However, petitioners obliquely suggested such an objection in the PSC Notice Re: UK Litigation at 2-3, stating that they would rest on the record developed in the three test

[78] Petitioners noted that they had requested that the special masters make a request for these documents directly to the U.K. court. As respondent had requested and received such reports without aid of the court, we placed the burden on petitioners to make a request for documents they deemed relevant on their own. It was clear at the conclusion of the *Snyder* hearing that the burden to make the request was petitioners. *See* PSC Notice Re: UK Litigation at 2.

cases, “a record including objections to the admission of evidence from the UK as was introduced during these hearings.”

Assuming, *arguendo*, that this reference is a belated objection to my consideration of any of the material released by the U.K. court, and testimony derived from such material, I overrule the objection. Whatever validity the “unfair” surprise and lack of time to prepare for cross-examination arguments had at the *Cedillo* hearing had evaporated by the time of the *Snyder* hearing five months later. Petitioners were free to request that Dr. Bustin return for additional cross-examination at either of the two test case hearings subsequent to *Cedillo*. Their failure to do so constitutes waiver.

With regard to their inability to examine any evidence underlying Dr. Bustin’s and Dr. Rima’s critiques of Unigenetics laboratory’s results, petitioners also waived any objection by their failure to request disclosure of such materials from the U.K. court. As the testimony discussed in Sections VII and VIII, below, makes abundantly clear, voluminous materials were filed with the U.K. court regarding the laboratory’s operations. Although Unigenetics is no longer in business, the U.K. court is. Given the amount of impassioned argument devoted to the petitioners’ need for such materials, petitioners’ failure to lodge a request for their disclosure in the months following all three Theory 1 hearings is inexplicable. It is also waiver.

Petitioners introduced a belated expert report from an entirely new witness, Dr. Karin Hepner, attesting to the validity and reliability of Unigenetics’ testing program. Equally belatedly, but with a far better excuse, respondent answered this evidence with filings from the U.K. litigation. By the time of the *Snyder* hearing, petitioners had not taken even the most basic steps to obtain what they contended was favorable evidence crucial to their case. Their July 31, 2008 filing, informing the court that they were no longer seeking to obtain this evidence from the U.K. court, waives any objection to the court’s consideration of the U.K. materials introduced. The issue of the weight I have accorded such evidence is addressed below.

Section II. Petitioners’ Theories of Causation.

Most opinions of the special masters who hear Vaccine Act cases begin with a discussion of the medical records and medical condition of the individual claiming the vaccine injury. Given the complexity of the evidence in this case and of the condition from which Colten suffers, I choose to begin with the general causation evidence. After evaluating that evidence, I discuss Colten’s medical history and treatment, and then apply the general causation evidence to Colten’s situation. Ultimately, the significance of specific aspects of Colten’s medical history, diagnosis, and treatment will be best understood after consideration of the general causation evidence.

In this section of the opinion, I first discuss the general theories of causation upon which Colten’s claim for compensation rests. In Section III, I set forth the applicable law and standards for adjudicating Vaccine Act Cases. Section IV is devoted

to explaining ASD. In Sections V-VII, I set forth and discuss the general causation evidence. Colten's own medical history appears in Section VIII. In Section IX, I apply the law to the facts of Colten's case and explain why I have concluded that petitioners have not met their burden of proof.

This method of proceeding in no way reflects any lack of importance for Colten's specific claim for compensation. As the court and counsel for both parties acknowledged at Colten's hearing, this case presents both a general causation theory and a specific causation claim. Snyder Tr. at 6-7, 16-17. The evidence developed in the general causation case was voluminous and complex, and Colten's specific situation can be best examined and understood in light of the scientific theories upon which it is based.

The court is deeply grateful to Colten and his parents for agreeing to have his case presented as one of the first three test cases on the combined theory of causation. Petitioners are caring and committed parents who have focused considerable time, effort, and financial resources on Colten's medical treatment, educational needs, and general welfare. No one who observed the hearing could doubt their commitment to Colten, or their good faith belief that Colten's condition is the result of his childhood vaccines. They have acted on that belief in determining many of the treatments Colten has received. In this respect, they mirror the anecdotal accounts of the struggles of many other parents of autistic children. However, in this court, as in all other courts, subjective belief is insufficient as evidence of causation. *See* § 300aa-13(a)(1).

Part V of Snyder Petitioners' Post Hearing Brief ["Snyder Pet. Post Hearing Br."], filed February 19, 2008, discussed both the general theory of causation and the evidence specific to Colten. Borrowing from the subheadings in the brief, the building blocks of their theory can be expressed as: (1) the ethylmercury in TCVs is an immune suppressant; (2) the attenuated measles virus contained in the MMR vaccine is an immune suppressant; (3) the combined effect of both TCVs and the measles vaccine virus suppressed the immune system of at least some children who received both; (4) this immunosuppression permits the measles virus to persist in these children; (5) a persistent measles virus can enter the brain and cause a neurological injury; and (6) that neurological injury can include autism or ASD symptoms. The theory itself is complex, implicating medical conditions and scientific disciplines ranging from epidemiology to virology.

Each of these building blocks has its own component parts. The evidence presented includes both uncontroverted facts (for example, that the measles virus may persist in some individuals) and vigorously litigated contentions (for example, that persistent measles virus can cause autism). It necessitates discussion of the reliability

of *in vitro* studies,[79] animal studies,[80] specific types of scientific testing and the laboratory in which some tests were performed. In addition to epidemiology and virology, it will be necessary to explore gastroenterology, genetics, immunology, molecular biology, pediatric neurology, and toxicology.

Although the OAP petitioners include children with many different diagnoses on the autism spectrum, the general causation theory presented in the Theory 1 test cases was limited to a specific type of ASD, one with regressive features. Regressive autism is discussed in more detail below, but in the context presented here, it represents a condition arising in the second year of life, after apparently normal development. In Colten's specific case case, petitioners relied upon the theory that the TCVs and MMR, acting in concert, caused Colten's condition, which was variously referred to as "autistic symptoms" or "regressive autism." *See, e.g.*, Pet. Post Hearing Br., pp. 6, 9. They did not advance a significant aggravation claim, instead contending that Colten was a healthy, happy child until receipt of his MMR vaccine. However, implicated in their theory is the underlying premise that Colten is one of a small minority of children who are "hypersusceptible" to the effects of the ethylmercury contained in some of his early vaccinations.

Although petitioners' explication of their theory began with evidence regarding mercury's effects on the immune system, I begin the discussion of the evidence presented with the evidence concerning ASD itself, followed by the evidence pertaining to mercury toxicology and immunology, measles virus and vaccine, and, finally, the specific aspects of Colten's case, testing, and treatments.

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[79] An *in vivo* study is one that is done in an intact animal or human being. *In vitro* studies involve cells taken from an animal or human that are grown in a petri dish and subjected to experimental conditions. The results from *in vitro* studies cannot be extrapolated to demonstrate what would happen *in vivo*. Cells in culture are in an environment metabolically very different from that within the intact subject. Cedillo Tr. at 2321-23. *In vitro* studies are useful for generating hypotheses. If a substance does not cause harm *in vitro*, then it will not cause harm *in vivo*. If it causes harm *in vitro*, then further study is warranted. Cedillo Tr. at 2324. The Institute of Medicine has acknowledged this scientific principle, commenting that "an adverse effect ... *in vitro* does not readily translate into a physiologic argument." Immunization Safety Review, VACCINES AND AUTISM, IOM, National Academies Press, 2004 ["IOM 2004 Report"], filed as Cedillo Res. Ex. JJ, at 140. Confronted with scientific evidence derived from *in vitro* studies, courts have required some supporting evidence indicating the results can be extrapolated. *See, e.g.*, *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 830 (D.C. Cir. 1988) (holding *in vitro* studies insufficient evidence of causation in humans in the face of overwhelming contradictory epidemiologic studies).

[80] Animal studies have limitations because the effects of a drug may differ in animals and humans. For example, saccharin causes cancer in rodents, but not in humans. Tylenol, even in extremely small doses, is lethal to cats. Cedillo Tr. at 2334. *See, e.g*, *Goewey v. U.S.*, 886 F. Supp 1268 (D.S.C. 1995) (neurotoxic effects of substance in chickens cannot be extrapolated to humans, absent some epidemiologic confirmation). *See also General Electric v. Joiner*, 522 U.S. 136, 144-45 (1997) (district court did not abuse its discretion in excluding animal studies that did not involve the same modes of exposure as in humans).

Section III. The Legal Standards to be Applied.

This section addresses the legal standards to be applied in general in Vaccine Act cases. The legal arguments concerning the application of these standards to Colten's specific case are addressed in Section VIII, below.

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. The petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the 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 v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). *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 a vaccine set forth on the Vaccine Injury Table; (2) received the vaccine in the United States; (3) sustained an illness, disease, disability, or condition caused by the vaccine (or experienced a significant aggravation of an illness); and (4) the problem has persisted for more than six months.[81] Vaccine litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or

[81] 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 four factors listed above, along with others not relevant to this case.

whether the symptoms have persisted for the requisite time. In this case, the focus, as in most 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.

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. 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. Courts, whether they deal with vaccine injuries, medical malpractice claims, toxic torts, or accident reconstruction, must 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 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). *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 v. Sec'y, HHS*, No. 99-653V, 2003 U.S. Claims LEXIS (Fed. Cl. Spec. Mstr. Sept. 26, 2003)); 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 is tipped. *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").

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 v. Sec'y, HHS,* 991 F.2d 1570, 1575 (Fed. Cir. 1993) (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).[82] 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.

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. Witness demeanor is an important, if subjective, factor. 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 factors in determining what testimony to credit and what to reject.

If merely an opinion supporting vaccine causation, without more, were all that is necessary to meet petitioners' 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 causation by presenting "factors unrelated."[83] 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 the 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.[84] In weighing and evaluating expert opinions in Vaccine Act cases, the

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[82] If the respondent were limited to presenting the matters set forth in § 300aa-13(a)(1)(B)–proving by a preponderance of the evidence that the petitioner's condition is due to a factor unrelated to the vaccine–any petitioner with a disease for which medical science has not yet discovered a cause would be at a distinct advantage in Vaccine Act litigation. Section 300aa–13(a)(1)(B) indicates that respondent may not rely upon "idiopathic, unexplained, unknown, hypothetical, or undocumentable" causes as a "factor unrelated."

[83] *See* § 300aa-13(a)(2).

[84] *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

same factors the Supreme Court considered important in determining their admissibility provide weights and counterweights. *See Kumho Tire*, 526 U.S. at 149-50 and *Terran*, 195 F.3d at 1316.

Section IV. Pervasive Developmental Disorders

A. Autism Spectrum Disorder and Its Core Features.

"Pervasive Developmental Disorder" is an umbrella term for a collection of disorders.[85] Pervasive developmental disorders include autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and PDD-NOS.[86] Although the terms PDD and ASD are often used interchangeably,[87] neither the term "autism spectrum disorder" nor "ASD" appears in the DSM-IV-TR. A PDD is defined by the DSM-IV-TR as a "severe and pervasive impairment in several areas of development: reciprocal social interaction skills, communication skills, or the presence of stereotyped behavior, interests and activities." This impairment must be "distinctly deviant relative to the individual's developmental level or mental age."[88] In this opinion, unless the context of the testimony, report, or other exhibit indicates that the witness or author was referring to a specific subtype of PDD, I will use the terms ASD or autism.[89]

All of the disorders falling within the autism spectrum are defined by a collection of symptoms or behaviors. With the exception of Rett's disorder,[90] all ASDs are diagnosed by comparing behavioral symptoms exhibited by a child against an established set of broad diagnostic criteria. The diagnosis is made by direct observation, videos of the child, and from parental reports, as there is no biochemical

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compensation); and § 13(b)(1) (special master not bound by any particular piece of evidence).

[85] "Disorder" is defined as "a derangement or abnormality of function." DORLAND'S at 547.

[86] Diagnostic and Statistical Manual of Mental Disorders, Fourth Ed., Text Revision, American Psychiatric Association (2000), at 69-84, ["DSM-IV-TR"]. The DSM-IV (the version preceding the most current "Text Revision" version) was filed as Cedillo Pet. Ex. P, Tab 41.

[87] Cedillo Tr. at 1263.

[88] DSM-IV-TR at 69.

[89] The term PDD is easily confused with PDD-NOS. For that reason, I use ASD instead of PDD, unless directly quoting from testimony or an exhibit. Some researchers do not include Rett's disorder or childhood disintegrative disorder in the umbrella term "ASD." *See* C. Johnson and S. Myers, *Identification and Evaluation of Children with Autism Spectrum Disorders*, PEDIATRICS, 120(5); 1183-1215, at 1184 (2007) ["Johnson and Myers"], filed as Snyder Res. Ex. DD, Tab 4.

[90] A genetic test for Rett's disorder exists. *See* P. Moretti and H. Zoghbi, *MeCP2 dysfunction in Rett syndrome and related disorders*. CURR OPIN. GENET. DEV. June; 16(3): 276-81 (2006), filed as Cedillo Res. Ex. FF, Tab 14.

test for ASD.

Autistic disorder or autism is the most severe form of the disorder; Asperger's syndrome is the least severe. Pervasive developmental disorder, not otherwise specified (the condition with which Colten was diagnosed), falls somewhere in the middle. Cedillo Tr. at 1588. Many researchers divide autistic disorder into classic or early onset autism[91] and regressive autism, with regressive autism having a later onset and involving the loss of previously acquired developmental milestones, particularly the loss of expressive language. Cedillo Tr. at 1288A-90A.

Children with autism or ASD are most symptomatic in the second and third years of life. While not all children follow the same pattern, in the second year of life (12-23 months of age), autistic children generally do not imitate others, have poor language, do not play well, are social loners, and do not interact with those around them. They may respond to the theme songs of favorite television shows, but not to their own name. If they are speaking, their vocalization is non-specific and babbling. By the time the child is three years old, speech is becoming echolaliac, repeating things other people have said or things they have heard.[92] Autistic children are interested in puzzle play, but not in symbolic or imaginative play. Cedillo Tr. at 1618-21.

As the children reach school age, there is a gradual improvement in function that may range from minimal to significant. However, relative to their typically developing peers, impairments in the core domains remain. Cedillo Tr. at 1621.

Doctor Wiznitzer testified that autism cannot be cured; any recovery is rarely complete. Less than 10% of his patients outgrow autism or reach the point when it does not interfere with their daily activities and allows them to function adequately within society. Cedillo Tr. at 1767-68. Some very small minority of children seem to outgrow ASD. Although they may have certain behaviors that are not entirely normal, they no longer fit the DSM-IV diagnostic criteria. Cedillo Tr. at 1696-98.

According to Dr. Fombonne's testimony and slides, the incidence of autism appears comparable across geographic lines. While different rates may be published for different countries, there is no evidence that the actual incidence is different. The incidence of autism is male biased, with a male to female ratio of four to one. Among high-functioning autistics, the ratio is much higher, at about six or eight boys for every girl. About 70% of children with autism are mentally retarded. The ratio of boys to girls in those with mental retardation is about 1.7:1. Although girls are less likely to be

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[91] Some researchers distinguish between early onset and classic autism, defining "early onset" as autism that manifests before six months of age, and defining "classic" as autism in which the symptoms manifest after six months of age and generally between ten and eighteen months of age. Cedillo Tr. at 1287A-89A.

[92] DORLAND'S at 585.

autistic, those with autism tend to be more severely afflicted and are clustered on the lower range of development. Children with a PDD-NOS diagnosis are probably less likely to be classed as mentally retarded (defined as an intelligence quotient under 70), but these figures are not well developed. About 20-30% of children with ASD have or will develop epilepsy over the course of their lives, often beginning during adolescence. In contrast, mentally retarded children often have seizures or epilepsy, but they develop the condition early in life. Cedillo Tr. at 1300A-03A; Cedillo Res. Tr. Ex. 8, at 18-19.

Considerable testimony was devoted to explaining how autism came to be recognized as a distinct disorder, how its definitions have changed, how it is now diagnosed, and what is known about its onset, causes, and pathophysiology. This evidence was primarily provided by the pediatric neurologists and geneticists, with Drs. Kinsbourne and Corbier testifying on behalf of petitioners and Drs. Wiznitzer, Cook, Fombonne, and Rust on behalf of respondents. The witnesses agreed upon many points. Where there was no genuine disagreement, their testimony is summarized below, generally without reference to the witness who supplied it.

There were several points of disagreement, however. The witnesses disagreed whether the rising prevalence of ASD constitutes an "autism epidemic" or even a significant increase in the percentage of children who suffer from the condition; whether differences in onset and some symptoms constitute separate phenotypes of autism with distinct (and different) causes; and the central question of whether vaccines can be placed properly on the list of differential diagnoses for causing autism.[93] In the discussion of the evidence below, I have indicated the areas of disagreement between the parties, and, to the extent necessary, why I have credited certain opinions while rejecting others.

B. History.

1. Early Descriptions of Autism: Kanner, "Refrigerator Mothers" and the DSM.

Autism is not a new disorder. Although the term "autism" was coined by Leo Kanner in a 1943 report about eleven children with social impairments and language deficits, descriptions of individuals with behaviors consistent with autism have appeared in literature as far back as the Middle Ages. Cedillo Res. Ex. P at 6-7; Cedillo Tr.

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[93] "Differential diagnosis" is the diagnostic technique of including possible causes for a patient's condition, then ruling out causes until one is left (or selecting the most likely cause from those remaining). It is a central feature of medical science. What is unstated in this process, however, is that the resulting diagnosis is valid only if the original list of possible causes is limited to causes properly "ruled in." That is, there must be some reliable scientific or medical basis for putting a cause on the list of possible causes in the first place. The first *Althen* prong encompasses this point by requiring petitioners to advance a reliable medical theory for vaccine causation. *See Althen,* 418 F.3d at 1278. *See also* Tiufekchiev *v. Sec'y, HHS*, No. 05-437V, 2008 WL 3522297 (Fed. Cl. Spec. Mstr. July 24, 2008) and *Ruggerio v. Warner Lambert Co.* 424 F.3d 249, 254 (2d Cir. 2005); Restatement (Third) of the Law of Torts: Liability for Physical Harm § 28 (2005).

1281A-82A. Asperger described the disorder that bears his name in 1944. Both Kanner and Asperger also noted that some parents of children with the described disorders had personality characteristics similar to the behavioral difficulties in their children, an observation that prompted Asperger to suggest a genetic component to the disorder. *See* A. Bailey, *et al., Autism: the Phenotype in Relatives*, 28 J. AUTISM DEV. DISORDERS 369 (1998), filed as Cedillo Pet. Ex. 61, Tab E.

In the 1960s and early 1970s, autism was seen as a psychiatric disorder. In 1967, Bruno Bettleheim published *The Empty Fortress: Infantile Autism and the Birth of the Self*, setting forth his belief that the emotional detachment seen in many autistic children was the result of poor parenting, specifically the mother's failure to bond with her infant. The rate of autism diagnosis was very low during this period, perhaps reflecting the social stigma attached to this "refrigerator mother" theory of causation.

The diagnostic criteria for autism spectrum disorders have evolved since the condition was first described by Kanner. In 1968, at the time of the initial epidemiologic studies of autism, the DSM had no provisions for childhood psychiatric disorders, which is what autism was then considered to be. Thus, there were no agreed-upon diagnostic criteria for the condition, other than those posited by Kanner. Cedillo Tr. at 2513A. *See also* Cedillo Res. Ex. HH at 22.

In England, in 1970, Dr. Michael Rutter developed criteria for diagnosing autism. Cedillo Tr. at 2513A. *See* M. Rutter, *Genetic Studies of Autism: From the 1970s into the Millennium*, J. ABNORM. CHILD PSYCHOL. 28(1): 3-14 (2000), filed as Snyder Pet. Ex. 113. In 1979, Lorna Wing and Judith Gould summarized many historic descriptions of children with impairments of social interaction, speech and language problems, and behavioral disorders involving repetitive and stereotypic movements. However, the primary focus of their research, filed as Cedillo Res. Ex. P, Tab 156,[94] was their systematic effort to survey the prevalence of what is now recognized as ASD, and to develop classifications for the disorder, based on the behavioral symptoms displayed.

In the U.S., the diagnostic criteria changed in 1980, when the diagnostic category of pervasive developmental disorder was added to DSM-III, and the diagnosis was shifted out of the childhood psychosis section of the DSM. In 1987, the diagnosis of PDD-NOS, was added to the DSM-III, further expanding the categories of autism diagnoses. In 1994, the DSM-IV was released. It reorganized the diagnostic criteria for autistic disorders, and added Asperger's disorder.[95] Cedillo Tr. at 2514A-15A.

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[94] L. Wing and J. Gould, *Severe Impairments of Social Interaction and Associated Abnormalities in Children: Epidemiology and Classification.* J. AUTISM DEV. DISORD. March; 9(1): 11-29 (1979).

[95] The DSM-IV-TR criteria now in use do not markedly differ from those in the DSM-IV. Editorial revisions were made to the PDD-NOS diagnosis to make the criteria more specific. Johnson and Myers, Snyder Res. Ex. DD, Tab 4, at 1185-86.

2. Rising Prevalence?

Doctor Fombonne testified that there are approximately 12 published studies on the prevalence of autism. The studies involve different investigators using different methods to examine autism diagnoses in the U.K., the U.S., Canada, and in Scandinavia and the Faroe Islands. All of the studies using multiple sources of ascertainment show the current prevalence of ASD as between 60-70 cases per 10,000 people. Cedillo Tr. at 2512-13.

There was general agreement among the witnesses that both the raw numbers of ASD diagnoses and the percentage of children with such a diagnosis have risen dramatically in recent decades. However, there was no consensus that the rise represents an autism "epidemic" or even a true increase in the incidence of the disease. Cedillo Tr. at 1547-48. The increase in ASD diagnoses is considered, by some, as evidence for vaccine causation. Petitioners draw parallels, if not causal connections, between the increasing proportion of children with ASD diagnoses and the expanded infant vaccination schedules and introduction of the MMR vaccine during the same time frame. They consider the increase to be circumstantial evidence that environmental changes, including expanded vaccinations, are responsible for the increased ASD diagnoses.[96] Cedillo Tr. at 1056A-58.

Doctor Kinsbourne testified that part of the increase undoubtedly represents changes in disease classification and better ascertainment, but doubted that these factors accounted for all of the increased number of children diagnosed with ASD. Cedillo Tr. at 1057A-58. In response, respondent offered the testimony of Drs. Fombonne, Cook, and Rust, and introduced a number of epidemiologic studies[97]

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[96] Absent other evidence linking these events (increased vaccinations and increased incidence of ASD), a statistical correlation between the two would be an example of the "ecological fallacy." An ecological fallacy occurs when a correlation between an agent and a disease in a group cannot be reproduced when individuals are studied. Reference Manual on Scientific Evidence, 2d Ed. Federal Judicial Center, 2000 "["Reference Manual on Scientific Evidence"] at 391.

[97] Epidemiology is the study of the distribution of disease in human populations and of the factors that influence that distribution. Cedillo Tr. at 2501. There are two major types of epidemiologic studies–the cohort study and the case-control study.

The cohort studies are also called incidence studies. They compare the new onset of a disease in two groups of individuals, with one group exposed to something and the other group unexposed. By following the two groups over a period of time, and measuring the incidence of the disease in the exposed and unexposed groups, it is possible to determine if the exposure played a role in the development of the disease. If the incidence of the disease is the same in both groups, the exposure is unlikely to have had an effect on the development of the disease. Cedillo Tr. at 2501-02.

A case-control study starts with a group of individuals with a disease and compares those individuals to a group without the disease. Working retrospectively, the investigator measures past exposures of both groups in order to find exposures that appear to be higher in the group with the disease. The exposures of the two groups are compared, producing what is called an "odds ratio," which is a

indicating that there is no reliable evidence of an actual increase in the incidence of ASDs. Doctor Fombonne agreed that prevalence rates for autism are higher now than in previous decades, but asserted that much, if not all, of the increase can be attributed to better ascertainment, revised diagnostic criteria, greater practitioner awareness, diagnostic substitution, and changes in educational policies. Cedillo Tr. at 2512-15A, 2521A-23A. In summary, respondent contended that there is inadequate data to establish that rates of autism are, in fact, rising.

There was general agreement on the rate of ASD in the U.S. The U.S. estimate of 60-70 cases per 10,000[98] was derived from data from 14 different states. Illustrating some of the problems in case ascertainment, the rates among the states surveyed were highly variable, with New Jersey having an incidence of 107 per 10,000.[99] In contrast, the rate in Alabama was 32-33 per 10,000, only 1/3 of the New Jersey rate. Cedillo Tr. at 2510A-12.

The diagnostic sources used affect the prevalence rates found. When multiple sources are used to identify or ascertain a diagnosis of ASD, the rate per 10,000 rises. One problem in comparing rates among studies is that studies use different ascertainment criteria, resulting in widely differing prevalence rates. Doctor Fombonne used four different studies in the U.S., published between 1999-2001, to demonstrate a 14-fold difference in the rate of ASD per 10,000. Cedillo Tr. at 2516A-20A; Cedillo Res. Ex. 21, at.8.

Referral statistics, particularly those involving classifications for educational services for ASD, are more reflective of the increased availability of services than of a real increase in rates. Prior to 1994, there was no requirement for school districts or

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measure of relative risk. Cedillo Tr. at 2502.

Two other types of studies are also used: prevalence studies (also called cross-sectional studies) and ecological studies. Prevalence studies look at a population at a single point in time, and assess all of the individuals in the sample for disease and the characteristics suspected to be associated with the disease. Cedillo Tr. at 2502-03A. Ecological studies look at rates of a particular disease over time and compare those rates to exposure levels over the same period. An example of an ecological study would be comparing unemployment rates and suicide rates. If suicide rates go up as unemployment rates also rise, that might indicate there is a relationship between the two events. The inferences that can be drawn from ecological studies are less strong than those from cohort or case-control studies because ecological studies rely on aggregated, rather than individual, data. In the example of suicide and unemployment, an ecological study would not look specifically at individuals who had committed suicide to ascertain their employment status at the time, but simply at aggregated population data. Cedillo Tr. at 2503A-04B.

[98] *See* Cedillo Pet. Ex. P, Tab 24, Centers for Disease Control and Prevention, *Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002,* MORBIDITY AND MORTALITY WEEKLY ["MMWR"] Surveillance Summaries 56 (SS-1) (February, 2007).

[99] This incidence rate reflects that 1.07% of eight-year-olds in New Jersey had an autism spectrum disorder.

states to report autism as a separate category for educational services. The number of children for whom special education services were provided increased dramatically after passage of the Individuals with Disabilities Education Act[100] ["IDEA"]. Cedillo Tr. at 2521A-23A. In Illinois, when school districts began classifying children with autism, the rate of children with the diagnosis increased 14,000 percent. Cedillo Tr. at 1549A.

Diagnostic substitution also accounts for some portion of the increase in ASD prevalence rates. A study published in 2005[101] examined the impact of the creation of an autism category for educational services statistics on the categories of mental retardation and learning disabilities that predated the 1994 addition of the ASD category. Examined nationwide, increases in the use of the ASD category were accompanied by a roughly similar decline in the use of the mentally retarded and learning disabled categories. As Dr. Fombonne explained, there was a significant downward deflection within the categories of mentally retarded and learning disabled during the period 1994-2003, after the separate category of autism was added. Cedillo Tr. at 2524A-31.

A survey article used as a trial exhibit by petitioners in *Cedillo* was, in most respects, supportive of Dr. Fombonne's testimony that the rising prevalence of autism diagnosis may be partially explained by diagnostic switching, artifact, and broadened diagnostic criteria.[102] However, the authors indicated that these factors may not account for all of the increasing prevalence, a conclusion shared by Dr. Fombonne.[103] Cedillo Pet. Tr. Ex. 15 at 6.

The evidence on the issue of rising prevalence was largely inconclusive. It neither supports nor refutes the central issue of vaccine causation.

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[100] Pub. Law 101-476, October 30, 1990, 104 Stat. 1103. Autism is one of 13 categories of disability identification established by IDEA. Prior to IDEA, autistic children could have been classified as mentally retarded or as having other health impairments, but there was no separate autism classification.

[101] P. Shattuck, *The Contribution of Diagnostic Substitution to the Growing Administrative Prevalence of Autism in U.S. Special Education*, PEDIATRICS 117(4): 1028-37 (2005), filed as Cedillo Res. Ex. P, Tab 161.

[102] Cedillo Pet. Tr. Ex. 15 at 6. (C. Newschaffer, *et al., The Epidemiology of Autism Spectrum Disorder*, ANNUAL REV. PUBLIC HEALTH 28: 235-58 (2007)).

[103] Doctor Fombonne also noted that the article omitted discussion of some additional factors that may account for some of the increase. Cedillo Tr. at 2638-39A.

C. Current Diagnostic Criteria.

1. Diagnoses Included in the Autism Spectrum.

Within the U.S., the standard diagnostic criteria are found in the DSM-IV-TR.[104] Because the criteria are very broad, children with the same DSM-IV diagnosis might present with very different symptoms. Moreover, the symptoms displayed by an individual child might change over time. In clinical presentation, children with the same diagnosis, including the same subgroup on the autism spectrum, may have different levels of severity of impairment. Cedillo Tr. at 1592-94. The key features of each DSM-IV classification within the PDD umbrella are summarized below.

a. Autistic Disorders.

To be diagnosed with autistic disorder, the DSM-IV requires that a child must display abnormal development in the three different domains of: (1) language and communication; (2) social interaction; and (3) repetitive patterns of play, behavior, or interests. Although the behavioral manifestations must occur before three years of age, the diagnosis itself may be made much later. Cedillo Tr. at 1263-64, 1591-92.

In the domains of communication and socialization, the impairment must be qualitatively significant. Cedillo Tr. at 1589-91. The behaviors must reflect six of the subcriteria in the three domains. At least two of the six subcriteria must be from the socialization domain; there must be at least one behavior from each of the other two domains. Cedillo Tr. 1265A-66A, 1617-18. Additionally, the behavior must constitute a functional impairment that actually causes problems in socialization, communication, and play. Finally, the behaviors must not be explainable by another medical or psychiatric disorder, such as Rett's disorder. Cedillo Tr. at 1618.

b. PDD-NOS.

If a child does not meet all of the diagnostic criteria for autistic disorder, then other diagnoses are entertained. A child who clearly meets the diagnostic criteria in two of the three domains, but has a dysfunction in the third domain that is not sufficiently severe to meet the diagnostic criteria, would be classified as having pervasive developmental disorder, not otherwise specified. Cedillo Tr. at 1592. Children who are diagnosed later in life are often given this diagnosis. In many cases, these children are

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[104] In Europe, the criteria are found in the 10th edition of the International Classification of Disease Manual ["ICD-10"]. The ICD includes the full range of medical disorders, with one chapter devoted to psychiatric disorders, including autism. That one chapter is the equivalent of the DSM-IV-TR. In most cases, the data collected lead to the same diagnosis under either the ICD-10 or the DSM-IV-TR criteria, and thus, studies using either criteria can be reliably compared. Cedillo Tr. at 2617A-19. Doctor Fombonne, who was part of the group that developed the diagnostic criteria for both manuals, testified that there are very few differences between them. Cedillo Tr. at 1280A-81A.

less severely affected than other children on the spectrum. Cedillo Tr. at 1274A-75A.

c. Asperger's Disorder.

Many of the highly functioning individuals with ASD are classified as having Asperger's disorder. In Asperger's, language develops normally. By two years of age, a child with Asperger's disorder might have a vocabulary of multiple words. Conversational impairments are subtle. Intelligence is in the normal range. However, those with Asperger's frequently display clear social impairments. Cedillo Tr. at 1275A-76.

d. Rett's Disorder.[105]

Rett's disorder is the only specific DSM-IV PDD diagnosis with a defined cause. This syndrome has been identified as a genetic disorder, caused by a defect in the MeCP2 gene.[106] It is a diagnosis almost exclusively limited to girls. After what appears to be normal development, the girls develop stereotypic movements, microcephaly, and other neurologic signs.[107] Cedillo Tr. at 1277A-78A, 1589.

e. Childhood Disintegrative Disorder.

In an extremely rare condition called childhood disintegrative disorder, development is normal, until about two or three years of age. When deterioration manifests, it does so with a dramatic loss of skills, and culminates in severe autism.[108] Cedillo Tr. at 1276-77A, 1589. This disorder was first described in the 1920s. Hazlehurst Tr. at 533A-34A.

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[105] Some exhibits and testimony use the term "Rett syndrome," omitting the apostrophe. I use the spelling found in the DSM-IV-TR.

[106] R. Amir, *et al., Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpGbinding protein, 2* NAT. GENET. 23(2): 185-88 (1999), filed as Cedillo Res. Ex. P, Tab 2; and P. Moretti and H. Zoghbi, *MeCP2 dysfunction in Rett syndrome and related disorders,* CURR. OPIN. GENET. DEV. 6(3): 276-81 (2006), filed as Cedillo Res. Ex. FF, Tab 14.

[107] B. Hagberg, *Clinical Manifestations and Stages of Rett Syndrome*, MENTAL RETARDATION DEVEL. DISABIL. RES. REV. 8: 61-65 (2002), filed as Cedillo Res. Ex. DD, Tab 6. The author, one of the first researchers to describe the condition, describes classical Rett's disorder as relatively normal development for the first six months of life, followed by delayed, but not significantly abnormal, development during the following year. The onset of clear developmental regression, with loss of acquired skills, occurs between the ages of one to four years. This regression is followed by a "pseudostationary period" during which some skills are regained, but an unapparent and slow neuromotor regression occurs. The final stage involves complete loss of ambulation. *Id.*, Table 3.

[108] For a more detailed description of this disorder, *see* E. Fombonne, *Prevalence of Childhood Disintegrative Disorder*, AUTISM 6(2): 149-57 (2002), filed as Cedillo Res. Ex. P, Tab 62.

2. Domains of Impairment.

a. Communication Domain.

Examples of communication abnormalities include language delay, lack of babbling in a communicative context, or lack of pointing or gesturing to communicate something other than needs or desires by the age of 8-12 months. In older children, or in high-functioning children, the types of communication abnormalities are different and may include idiosyncratic sentences and a literal understanding of words. Cedillo Tr. 1266A-69A.

Lack of, or delay in, language development does not include children who point, gesture, or mime in an effort to communicate. An inability to initiate or to sustain a conversation can indicate a marked qualitative impairment of communication in children who have an otherwise adequate vocabulary. Such children might sing a jingle from a restaurant advertisement to communicate that they are hungry or want to go to a particular restaurant, rather than asking to go there. Children who repeat conversations, as if from a script, demonstrate a stereotyped or repetitive use of language. Cedillo Tr. at 1603-04.

b. Impaired Social Interaction Domain.

There are four subgroups within the impaired social interaction domain: (1) marked impairment in the use of multiple nonverbal behaviors; (2) failure to develop peer relationships appropriate to the child's developmental level; (3) marked impairment in expression of pleasure in the happiness of others; and (4) lack of social or emotional reciprocity. Nonverbal behaviors include gestures, eye contact, and use and understanding of body language. The subgroup of peer relationships takes into consideration a child's cognitive impairment, and looks to the nature of relationships appropriate for the level of developmental function, rather than calendar age. The third subgroup is essentially a deficiency in empathy. The last subgroup, social reciprocity, includes responding to contact from others, as well as initiation of social or emotional contact. Cedillo Tr. at 1594-96.

Social interaction abnormalities in infants and young children include poor eye contact, lack of social smiling, poor response to the child's own name, and reduced facial expressions. Cedillo Tr. at 1269A-70A.

The greatest impairments in socialization are in those children who are socially unavailable. They remain oblivious to their surroundings, do not seek consolation when injured, and may wander aimlessly. Social unavailability manifests at around 18 months to two years of age. Cedillo Tr. at 1597-98.

Spontaneous play is evaluated at the level of the child's mental and emotional functioning. Autistic children may play in a repetitive manner or fail to initiate play at all.

Cedillo Tr. at 1604-05. Socially remote children do not initiate social interaction with an adult. They may respond if an adult initiates contact, but will not seek to continue the contact if the adult breaks away. These children look at their peers, but do not approach them, and often choose to play alone. Cedillo Tr. at 1598-99.

Other autistic children, especially older ones, may engage in socially inappropriate interaction, particularly with their peers. Autistic children with normal intelligence may display more social skills, but their behavior is mechanical and scripted and interaction may be focused on their own narrow range of interests or on learned responses. To illustrate a learned response, Dr. Wiznitzer described a child who could not answer a question about where he lived, but could answer correctly when asked for his address. Cedillo Tr. at 1599-1602.

c. Restricted, Repetitive, and Stereotyped Behavior Domain.

The third diagnostic criterion requires that the child display restricted, repetitive, and stereotyped patterns of behavior falling in at least one of four subcategories: (1) an abnormally restricted pattern of interest; (2) an adherence to specific (and non-functional) routines or rituals; (3) stereotyped and repetitive motor mannerisms; and (4) persistent preoccupation with parts of objects. Cedillo Tr. at 1612-16.

The restricted patterns of interest criterion, the first in this subgroup, is an intense preoccupation with narrow, restricted subjects, ranging from watching fan blades turn to an overwhelming interest in a cartoon character, a card game, or an area of natural history. Cedillo Tr. at 1613-14. A normal child might watch a ceiling fan for a few seconds, but an autistic child might spend thirty minutes looking at the fan and would be angry at attempts to redirect his interest. Cedillo Tr. at 1271A-72A. One autistic child might be fascinated with Star Trek, while another might focus on numbers and letters. It is the fact of the restricted interest, not the subject matter of the interest, that is important for the diagnosis. Cedillo Tr. at 1593A. An autistic child might repetitively turn a light on and off for a lengthy period of time; in contrast, a typically developing child might do so for a few minutes before moving on to another interest. Cedillo Tr. at 1616.

The second subgroup, an adherence to routines, is an apparent desire for sameness: the same seat at the dinner table, taking the same route to a location, or expecting the same greeting ritual. Cedillo Tr. at 1614-15. By two or three years of age, there is a lack of imaginary or pretend play and a tendency to line up toys or other objects. Cedillo Tr. at 1270-72. This compulsive behavior criterion is different than an obsessive-compulsive disorder in terms of the quality of the behavior. Cedillo Tr. at 1616.

The third subgroup, repetitive motor mannerisms, includes the hand and finger examination called “hand regard.” Autistic children may clap or flap their hands in a manner not common to normal infants or toddlers. Cedillo Tr. at 1270-72, 1615. They

may engage in ritualistic actions, including twirling around or touching objects in a repeated pattern. Cedillo Tr. at 1615.

The fourth subgroup involves a focus on individual components of an object, rather than the object itself. For example, an autistic child might not be interested in playing with a toy car; instead he might focus on making the wheels spin. Cedillo Tr. at 1615-16.

3. Diagnostic Tools.

Specialized checklists and interview instruments are used to evaluate children for ASD. The Childhood Autism Rating Scale ["CARS"] has been used for many years. More recent rating systems include the Autism Diagnostic Interview-Revised ["ADI-R"] and the Autism Diagnostic Observational Schedule-Generic ["ADOS-G"]. The ADI-R is an interview of the caregiver; the ADOS-G is used in direct examination of the child. These two instruments are used together. Cedillo Tr. at 1272A-74A. These standardized tests allow for a high degree of agreement among clinicians in the diagnosis of ASD. Cedillo Tr. at 1274A.

Although most autism specialists use one or more of the checklists in making a diagnosis, they also use home videos to observe behaviors that a child may not manifest in the clinic. Home videos of babies at age 10-12 months have proven extremely useful in identifying autistic children early in life.[109] Several studies have established that a trained observer can distinguish children with autism from those with mental retardation (of a type not identifiable by facial characteristics) and from children with typical development. The primary features distinguishing autistic children from their mentally retarded or typically developing peers are abnormal gaze or eye contact, deficits in joint attention, and lack of orientation to their name. The single best predictor of an eventual autism diagnosis is a baby's failure to look at people trying to interact with him. Cedillo Tr. at 1296A-99A. Home videos, although useful as diagnostic tools, are not used as the sole basis of a diagnosis of ASD. Cedillo Tr. at 1699-1700. Video analysis done with children younger than 12 months can over-diagnose autism, but even the children improperly diagnosed with autism may have other developmental issues. Cedillo Tr. at 1724-25. Several of these studies are discussed in more depth below.

The precise onset of the disease of autism is difficult to determine. The first

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[109] Several of the pediatric neurologists testified that they used home videos in their diagnosis of children with autism. Cedillo Tr. at 1295A-99A,1643-45, and 1756-59. Interestingly, Dr. Kinsbourne's first foray into the use of home videos to detect symptoms of autism was in Michelle Cedillo's case. He testified that he observed no signs of autism in Michelle Cedillo's videos taken prior to her MMR vaccination. Cedillo Tr. at 1064-66A, 1171. Other experts who viewed the videos pointed out specific portions of the videos that demonstrated early onset or classic symptoms of autism in Michelle months prior to her MMR vaccination. Cedillo Tr. at 1338A-54.

symptoms are often observed before 24 months of age. However, recognition of these symptoms does not necessarily indicate the beginning of the disease process. To analogize to lung cancer, the first recognized symptom might be coughing blood, but by that point, the cancer has been in the lungs for many months to years. Cedillo Tr. at 1283-84. With autism, some parents have reported that their child appeared to be developing normally, but at age 12-24 months, they began noting problems in language development, as compared to other children of similar age. Thirty percent of parents recognize some developmental problem by the child's first birthday; rising to 80% by the child's second birthday. The mean age of first parental concern about the child's development is approximately 14-19 months. Cedillo Tr. at 1285A-86A.

D. Separate Phenotypes?

Doctor Fombonne testified that the epidemiology of autism is complicated by the various classifications used, such as classic autism, early onset autism, and regressive autism. Cedillo Tr. at 2596-97. It is not only the epidemiology that is complicated by these classifications; the classifications affect the causation arguments as well.

Petitioners' theory of causation involves the MMR vaccine triggering onset of autism in a group of children with a separate phenotype[110] of the disorder. For a number of reasons, their theory requires that regressive autism be a separate phenotype. Some of those reasons are based on the nature of the hypotheses developed. The temporal connection between MMR vaccination and loss of skills was cited by Dr. Kinsbourne as evidence of a causal mechanism occurring shortly before the time of loss. Skill loss is often noted at around 18 months of age, shortly after administration of the MMR vaccine at 12-15 months,[111] thus making the MMR vaccine a possible candidate as a cause. Other reasons for the focus on regressive autism are more practical. Because the first symptoms of autism often precede administration of the MMR vaccine, it would be illogical to ascribe MMR causation to these cases.[112] Thus, an MMR theory of causation requires that regressive autism be considered a separate disorder, with a cause or causes distinct from the causes of early onset or classic autism. If regressive autism is not a separate phenotype, then it is more likely

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[110] Phenotype, as used in this context means: "the entire physical, biochemical and physiological makeup of an individual as determined both genetically and environmentally...". DORLAND'S at 1421. As used in the context of petitioners' theory, the phenotype of regressive autism (or regressive autistic enterocolitis) refers to a postulated "separate type" of autism with distinct features and causes separate from classic or early onset autistic disorders. Hazlehurst Tr. at 662A-64. The enterocolitis aspect of this theory is discussed in Section VI., Parts A.1.b and A.2.a.

[111] Since 1998, the Advisory Committee on Immunization Practices has recommended administration of the first dose of the MMR vaccine at 12-15 months of age. *See* MMWR, CDC; 55(22): 629-30 (2006). Prior to 1998, the recommendation was that the vaccine be administered at 15 months. *See* MMWR, CDC; 47(8):1-57 (1998).

[112] Doctor Kinsbourne would not opine in favor of causation if symptoms of autism preceded the MMR vaccination. Snyder Tr. at 536A-37A.

that regressive autism and classic autism share a set of common causes.

This section examines the evidence for regressive autism constituting a separate phenotype of autistic disorder. Thereafter, I consider what is known about the causes of autism in general. Finally, I return to regressive autism in particular to see if it is sufficiently different from classic or early onset autistic disorders, so as to render a separate cause for regressive autism likely or probable. Based on what is known about autism's strong genetic basis, the prenatal nature of significant changes in the pathophysiology of autistic brains, and the epidemiologic evidence, I conclude that there is insufficient evidence to show that regressive autism is a separate phenotype.

1. Possible Phenotypes of Autistic Disorder and PDD-NOS.

As the wide range of behavioral manifestations discussed in Part C, above, suggests, there is considerable variability in the presenting symptoms of ASD. Children with autistic disorder or PDD-NOS share similarities and display differences, regardless of their classification as "classic" or "regressed." However, according to Dr. Kinsbourne, the age at which symptoms of autism manifest, and the nature of the symptoms themselves, suggest that autistic disorders may be divided into several phenotypes: (1) early onset or congenital cases, in which children fail to reach developmental milestones and display some characteristic symptoms of autism in the first six months of life; (2) classic autism, in which early development is normal or near normal, until the first recognized symptoms of autism manifest, usually at ten to fifteen months of life; and (3) regressive autism, in which previously acquired skills are lost, usually during the second year of life. Cedillo Tr. at 1054-55.

Some of the research conducted into autism looks at early or classic autism as one category and regressive autism as a separate category. Much early research was criticized because it did not distinguish between children with regressive autism and those with classic or early onset of symptoms. Therefore, many researchers ensure a wider acceptance of their research by collecting data based on the nature of the onset of the disorder. This categorization should not be read to suggest that the researchers consider them to be two separate disorders.

a. Early Onset and Classic Autistic Disorders.

Some children with diagnoses on the autism spectrum demonstrate "early onset," in which abnormalities in development appear at around six months, when the child does not babble, does not respond to caregivers, and does not make eye contact.[113] The second group comprises the majority of children with an ASD diagnosis. This group of children seems to develop normally up to a certain point, but at 12-14 months, they have a progressive deviation of their development from the

[113] Doctor Rust testified that children diagnosed with autism during the first year of life are often classified as having congenital or classic autism. Hazlehurst Tr. at 459A.

normal curve. They cease acquiring skills, in contrast to their typically developing counterparts. Cedillo Tr. at 1287A-88A. The deviations in development observed during this period may become apparent at this time simply because the complexity of a child's interactions with his environment. Between the ages of six to twelve months, these interactions increase, providing more opportunities to observe abnormalities in development. Hazlehurst Tr. at 459B. The average age at which parents develop a concern about their child's development is higher when the child with ASD is a first child, rather than a second or later child; experienced parents are more likely to notice a deviation from the norm than inexperienced ones. Cedillo Tr. at 1669-70A. *See also* Cedillo Res. Ex. P at 11 and A. De Giacomo and E. Fombonne, *Parental recognition of developmental abnormalities in autism*. EUR. CHILD. ADOLESC. PSYCHIATRY September; 7(3): 131-36 (1998), filed as Cedillo Res. Ex. P, Tab 36 (presence of an older sibling associated with a lower age of affected child at time of first medical consultation for developmental abnormality).

b. Regressive or Loss of Skills Autistic Disorders.

Some autistic children experience a loss of previously acquired skills and are frequently referred to as having regressive autism. These children may have had apparently normal development prior to the loss of skills, but in about 70% of them, there was some earlier abnormality in development. Cedillo Tr. at 1289A.

2. Regressive Autism as a Distinct Disorder?

If the loss of skills (regressed) group and the early onset group are truly distinct phenotypes, then it is possible that there are different causal mechanisms for each type. Or, as Dr. Kinsbourne asserted, regression indicates that "something" is happening to the brain at the point when the regression manifests, with his implication being that the MMR vaccine is the postulated triggering event. Cedillo Tr. at 1055. Doctor Kinsbourne contended that there must be an explanation for why development in a normal or nearly normal child takes a sudden downward trajectory. He argued that "something must have most likely happened to change the trajectory of development in such a radical way." Snyder Tr. at 479A-80A. He testified that what causes autistic regression is "not only not known, it's hardly been investigated." Snyder Tr. at 480A.

Although there is still debate about the percentage of children with autistic disorders who manifest with loss of skills, most autism experts accept that skill loss does occur. That such skill losses occur in autistic disorders should not be surprising, because other conditions on the autism spectrum manifest with skill losses at specific time frames. Children with childhood disintegrative disorder experience a dramatic loss of acquired skills at three years of age or later, and girls with Rett's disorder also experience several periods of skill loss, involving both language and motor skills. The loss of skills also occurs in children with the PDD-NOS diagnosis in numbers similar to those with an autistic disorder diagnosis; in both cases, the skills loss generally occurs before the age of two. Cedillo Tr. at 1289A-90A.

a. Problems in Documenting Skill Loss.

Documentation of the nature and extent of skill loss in children with autistic disorder or PDD-NOS is complicated by the retrospective nature of case ascertainment in most studies, concerns about possible reporting bias in parental observations, and the lack of a standard measurement for regression. There is general agreement that some children with autistic disorders experience a loss of previously acquired skills, usually at 15-24 months of age.[114] Loss of language skills is most frequently observed, but skill loss may also occur in nonverbal areas of development. What percentage of autistic children fall in the regressive or loss of skills category is difficult to determine, with estimates ranging from 5 to 50%.[115] This wide range undoubtedly stems from the use of different criteria in classifying children. The range of estimates may be affected by recall bias, as parental interviews, conducted months or years after the onset of symptoms, were often the only method available to investigators to classify children as having experiencing regression.[116] Few of the earlier studies separated children with regression from those without. Cedillo Tr. at 1055-56A.

b. Use of Home Videos in Documenting Differences.

The use of home videos to screen children provided a method to classify children without recall bias affecting the classification. Werner and Dawson[117] and Osterling,[118] among other researchers, used videos of first and/or second birthdays to

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[114] *See* Cedillo Res. Ex. P, Tab 155, at 889 (E. Werner and G. Dawson, *Validation of the Phenomenon of Autistic Regression Using Home Videotapes*. Arch. Gen. Psychiatry 62(8): 889-95 (2005) ["Werner and Dawson 2005"]. Doctor Fombonne also testified that the loss of previously acquired skills is generally noted between 15-24 months of age. Cedillo Tr. at 1288A-89A.

[115] Cedillo Res. Ex. P, Tab 155, at 889 (Werner and Dawson 2005) (citing several studies with estimates ranging from 20-47%). Doctor Fombonne testified that approximately 20% of children experience a loss of skills without prior abnormal development. Cedillo Tr. at 1289A-90A. A chart in Dr. Fombonne's report (Cedillo Res. Ex. P at 45) lists six studies, performed between 1966 and 1998, measuring the percentage of children with regression. The results ranged from 22% to 50%. Although Dr. Fombonne indicated that the chart was from an article by Rogers, listed as Cedillo Res. Ex. P, Tab 131, it is the same chart that appears in Cedillo Res. Ex. P, Tab 60, E. Fombonne and S. Chakrabarti, *No Evidence for A New Variant of Measles-Mumps-Rubella-Induced Autism*, PEDIATRICS 108(4): 1-8 (2001) at 3 ["Fombonne and Chakrabarti"].

[116] It is not uncommon for parents to describe a loss of language in their children. However, in at least some of these cases, the children were not using language independently, merely imitatively. That is, the child repeated what the parent said, and the parent interpreted that as the use of a word. This is not a true loss of language, and the child's later lack of repetition does not represent autistic regression. Cedillo Tr. at 1668-70; Hazlehurst 460A-61A.

[117] Cedillo Res. Ex. P, Tab 155.

[118] J. Osterling, *et al., Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation*, DEV. PSYCHOPATHOL. 14(2): 239-51 (2002), filed as Cedillo Res. Ex. P, Tab 116.

measure behavioral differences between two groups of children diagnosed with ASD: those whose parents reported either (1) early onset or (2) regressive symptoms.

In both studies, typically developing children were used as the control group. The Werner and Dawson study demonstrated significant communication differences at 12 months among children with regression, children with early onset, and typically developing children. Children with regression were more verbal at 12 months than both the early onset and typically developing children. Children with early onset used declarative pointing less than the typically developing group. The regressed and the typically developing groups did not differ significantly in declarative pointing.

In the Werner and Dawson 2006 study, evidence of regression, or at least a dramatic slowing of language acquisition skills, manifested by 24 months of age. At that point, the typically developing children used significantly more words than either of the two ASD groups and were more likely to use declarative pointing. Both ASD groups demonstrated a significant worsening of social gaze between the ages of 1-2 years. *Id.* at 889, 891-94.

The Osterling study, a small retrospective case-control[119] study of infant behavior, also demonstrated differences between children classified as having early onset autism and those who experienced regression. Twenty children with ASD diagnoses were compared to 14 children diagnosed with mental retardation and 20 typically developing children. Parental interviews were used to establish time of onset of ASD symptoms. In 13 of the 20 ASD children, symptoms were noticed by 12 months of age and these children were classified as having early onset ASD. The remaining seven children experienced a loss of skills between 18-24 months of age and were classified as having regressive autism.

Using home videotapes and a behavioral coding system,[120] raters, who were blinded as to the children's diagnoses, were asked to rate behaviors and to determine to which group a child belonged. The behavior of early onset ASD children was compared to those with late onset, revealing differences between the two groups. Infants with regression had higher levels of: (1) orienting to name, (2) looking at objects held by others, and (3) looking at others than did early onset ASD infants. Compared to

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[119] A case-control study compares a group with a disease or condition to a control group without the condition. The term "retrospective" is applied to such studies because they begin after onset of the condition being studied and look backwards toward possible causal factors. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 388.

[120] The behaviors involved gaze (attention to people, looking at faces, and looking at an object not held by another), joint attention behavior (looking at an object held by another, alternating gaze between person and object, and pointing), communication and language development (vocalizing, babbling, and gesture), and social behaviors (seeking contact with an adult, participating in a game such as peek-a-boo, immediate imitation, and orienting to name being called). Motor behaviors consisted of repetitive motor actions, sitting unassisted, crawling, pulling up to a stand, standing unassisted, and walking.

early onset ASD infants, infants with regression did not display the social impairments at 12 months of age that the early onset children displayed. Osterling, Cedillo Res. Ex. P, Tab 116.

However, both groups of infants with ASD demonstrated significantly less gesturing, orienting to name, looking at objects held by others, and looking at people, than did the typically developing children. The ASD infants as a whole also demonstrated significantly more repetitive actions. Cedillo Res. Ex. P, Tab 116. The behaviors that best distinguished the ASD group from other groups were orienting to name, looking at objects held by others, and looking at people. *Id*.

Although both of these studies demonstrated behavioral differences between the children with early onset and regressive autism, the nature of the behaviors observed in both ASD groups was similar. Furthermore, the behavior of both ASD groups was distinguishable from that of typically developing children.[121]

The children classified as regressed appeared to have advanced language skills at 12 months of age, as compared to their typically developing peers or those with an earlier onset of symptoms. However, children who present with regression are more likely to be more severely afflicted by the disorder as they age. Snyder Tr. at 728A.

3. Classification Criteria.

The criteria for classifying children as having regressive autism are now standardized by most researchers. To be classified as having an actual loss of language, a child must have used at least five different words other than “mama” or “dada” in a meaningful way on a daily basis for at least three months. This requirement distinguishes true loss of language from the chance repetition of sounds on an occasional basis. Problems with classifications may still arise because the assessment of regression is still subjective and based primarily on parental reporting. Cedillo Tr. 1291A-93.

4. Conclusion.

The evidence indicates that children with autism who experience regression do not differ markedly from children who do not experience a loss of skills. Like children with childhood disintegrative disorder, they may be more severely afflicted in general, but the behaviors they display after regression look like the same behaviors as children with classic autism. The mean age of onset of the first symptom in children with autism, whether or not the children display regression, is within 12-17 months of age. Cedillo Pet. Ex. P, at 12-13.

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[121] The videotape scores correlated with the classification of the infants correctly 85% of the time.

Although it is clear that regression does occur, regression may not be the first sign or symptom of an autistic disorder. It may simply be the one most apparent to parents. I adopt the testimony of Dr. Fombonne that regressive autism is a clinical subtype used to index the trajectory of development in children with a formal diagnosis of PDD-NOS or autistic disorder. Cedillo Tr. at 1288A-89A. His testimony was supported by the Richler study, filed as Cedillo Res. Ex. DD, Tab 12,[122] and his own research. *See* Fombonne and Chakrabarti, Cedillo Res. Ex. P, Tab 60. The Richler study concluded that children with ASD and regression are a heterogeneous group with varying trajectories of development. The Fombonne and Chakrabarti study compared scores on the ADI-R for children with and without regression and found no statistically significant difference between the two groups in any domain, finding instead great similarity in the symptoms displayed. The group with regression did appear to have lower cognitive functioning when intelligence quotient scores were examined. *Id.* at 5.

I also adopt the testimony of Dr. Wiznitzer that the behaviors of a child with regression would not differ from a child with classic autism at 30 months of age, even if the age of onset of autistic behaviors differed markedly. Snyder Tr. at 728A. As he explained, there is no evidence to indicate there are any differences in brain anatomy between a child with regressive autism and one with classic autism. Snyder Tr. at 729A.

I thus conclude that petitioners have failed to demonstrate that regressive autism is a separate phenotype of ASD. The weight of the evidence is that some children with ASD develop symptoms by six months, others at 10 to 12 months, others at 18 months, and still others at three to four years of age. The "first" symptoms do not define the disorder; they simply indicate when the disorder manifests. Loss of language or other skills constitutes a clear and dramatic demarcation point, but, sadly, the skills loss presages the development of additional behavioral abnormalities. Other, more subtle deviations from normal behavior most likely preceded the skill loss. Regressive autism's features are not clearly distinguishable from classic autism. The symptoms displayed by those with autistic disorders appear more like a continuum than the separate bands Drs. Aposhian and Kinsbourne advocated. Cedillo Tr. at 197A, 1054-60. The weight of the evidence is that children with regression have no developmental or clinical characteristics that distinguish them from children without regression, and, thus, there is insufficient evidence for an etiologically distinct phenotype.

E. A Separate Cause?

Assuming, *arguendo*, that regressive autism is a separate phenotype, it does not

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[122] J. Richler, *et al., Is There a 'Regressive Phenotype' of Autism Spectrum Disorder Associated with the Measles-Mumps-Rubella Vaccine? A CPEA Study.* J. AUTISM DEV. DISORD. DOI 10.1007/s10803-005-0070-1: 299-316 (2006) ["Richler 2006"], filed as Cedillo Res. Ex. DD, Tab 12. I note that this was one of the articles cited most often in the expert reports filed in the Theory 1 litigation.

necessarily follow that it is etiologically distinct. The expert witnesses[123] were in agreement that autism is a strongly and complexly genetic condition. There was also general agreement that prenatal exposures to some infections[124] and drugs[125] are causally associated with autism. Even some infections in adulthood can lead to the development of autistic-like conditions.[126] What remains in dispute is the extent, if any, to which post-natal environmental factors play a role and what those factors might be. Thus, the disagreement primarily concerns whether autism has triggers, what those triggers are, and when they occur.

Some autistic syndromes have a known cause. Most of these well-studied syndromes have clinical features that meet the ASD diagnostic criteria, but the behaviors displayed differ in quality from those in idiopathic ASD. Cedillo Tr. at 2559A-60A. Although Fragile X children meet the criteria for autistic disorders, their behavior is different from autistic children without Fragile X syndrome.[127] Boys with Fragile X syndrome suffer from gaze avoidance, attention deficits, hyperactivity, and a high rate

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[123] Although several witnesses discussed the role of genetics in autism, the most highly qualified witness was Dr. Cook, with 23 years of research experience into autism's genetics.

[124] Congenital rubella is associated with disorders on the autism spectrum. Doctor Rust testified that children with congenital rubella have autistic manifestations, but have additional abnormalities not shared by most children with autism. Hazlehurst Tr. at 464A. Postnatally, autistic features have developed in previously normal children in the course of an acute encephalopathic illness. In two reported cases, the illnesses subsided and the autistic features disappeared. In a third case, involving an 11 year old child, a herpes virus infection was identified and specific areas of brain damage were identified by EEG and tomography scan. The patient did not fully recover. G. DeLong, *et al., Acquired Reversible Autistic Syndrome in Acute Encephalopathic Illness in Children*, ARCHIVES OF NEUROLOGY 38: 191-94 (1981), filed as Cedillo Pet. Ex. 61, Tab V. A case report of this third child also appears as Cedillo Pet. Ex. 61, Tab AA (M. Ghazinddin, *et al., Autistic symptoms following herpes encephalitis*, EUR. CHILD ADOLESC. PSYCHIATRY 11(3):142-46 (2002).

[125] Research associating autism with maternal exposure to thalidomide between day 20 and day 23 of gestation was discussed in I. Hertz-Picciotto, *et al., The CHARGE Study: An Epidemiologic Investigation of Genetic and Environmental Factors Contributing to Autism.* ENVIRON. HEALTH PERSPECTIVES 114(7), 119-25 (2006), filed as Cedillo Pet. Ex. 61, Tab HH. Prenatal exposures to several other drugs, including misoprostol, valproic acid, and possibly Terbutaline, increase the risk of autism. Cedillo Tr. at 2725A-26A.

[126] Doctor Kinsbourne testified that individuals with herpes or cytomegalovirus encephalitis may develop autism at an age far older than is typical. Cedillo Tr. at 1053A. From an examination of the case reports contained in his expert report, it would be more accurate to say that they develop symptoms or behaviors that are similar to, or congruent with, the core features of autism. *See, e.g.*, I. Gillberg, *Autistic Syndrome with Onset at Age 31 Years: Herpes Encephalitis as a Possible Model for Childhood Autism*, DEVELOP. MED. AND CHILD NEUROLOGY 33: 912-29 (1991), filed as Cedillo Pet. Ex. 61, Tab BB.

[127] Fragile X syndrome is an X chromosome-linked genetic disorder associated with mental retardation and dysmorphic features in males and with mild mental retardation in females. DORLAND'S at 1818.

of mental retardation. They also have a dysmorphic syndrome.[128] Children with tuberous sclerosis and congenital rubella also have specific types of physical and behavioral features that differ from children with classic autistic disorders. Cedillo Tr. at 2560A.

Doctor Kinsbourne testified that those working in the field of autism recognize that autism has numerous causes. He described the many different syndromes that have "an autistic outcome" as a functional convergence, in that different brain injuries may result in similar symptoms. He agreed that autism clearly has some genetic basis, but noted that in 80-90% of cases of autism, no single gene can be identified as causal. He asserted that strong genetic predispositions are affected by environmental interactions that may be prenatal or postnatal, and may include infections, vaccinations, and toxic agents. Cedillo Tr. at 1048-53A. Doctor Kinsbourne called autism's genetic basis "a susceptibility and not a predestination to autism." Cedillo Tr. at 1051A.

Respondent's experts agreed that something is happening in the brains of regressive children at the time of regression, but disagreed with Dr. Kinsbourne that what is happening is the result of a contemporaneous or temporally associated "trigger" for the regression. Respondent's position is that a vaccine cannot be responsible, *inter alia*, because of the evidence demonstrating autism's strongly genetic basis and prenatal origins. In the cases involving a known environmental influence (drugs and specific types of infections), the influence was prenatal, not post-natal. Further, the differences between autistic brains and those of typically developing controls found on autopsy strongly suggest that the brain pathophysiology in autism occurred prenatally, not postnatally.

1. Genetic Basis.

At the outset, it is important to understand the distinction between inherited genetic conditions and those that arise *de novo*. Autism has features of both types of genetic disorders.

The simplest form of an inherited condition is one which occurs when the child inherits a dominant gene from one parent. Huntington's chorea[129] is a devastating and ultimately fatal condition that is inherited in this manner. Other genetic conditions, such as sickle cell disease,[130] may require the inheritance of a defective gene from both parents.

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[128] "Dysmorphic" means malformed, resulting from a congenital anomaly. DORLAND'S at 575.

[129] Huntington's chorea is a progressive disease characterized by highly complex, involuntary jerky movements and mental deterioration culminating in dementia. Onset usually occurs in the 4th decade of life, with death occurring within 15 years of onset. DORLAND'S at 357; Cedillo Res. Ex. P at 14, ¶ 38.

[130] DORLAND'S at 79.

Still other genetic conditions arise *de novo*. In such cases, the genes that control the condition are not inherited from a parent. During conception or early gestation, defects or mutations in genes or chromosomes may arise, with or without a known cause. For example, Down's syndrome[131] is a genetic condition, but not one which is inherited. It occurs *de novo*, caused by an extra copy of half of chromosome 21. If a condition is inherited, theoretically at least, the parents can be tested for it, as can the child. If the condition arises *de novo*, only genetic testing of the child can reveal the defect. Cedillo Tr. at 1504-05. In Down's syndrome, testing of the parents would provide no indiction that a fetus has the condition. Before birth, testing the fetus is the only method to determine if the genetic defect is present.

Thus far, the examples of genetics have been simple ones. However, the genetics of autism are extremely complex, involving, in most cases, between three and twenty genes that interact. Cedillo Tr. at 2593A-94A. It also involves *de novo* genetic deletions and duplications.[132]

In about 10% of children with behavioral symptoms that meet the DSM-IV-TR diagnostic criteria for ASD, a specific, and primarily genetic, cause can be identified.[133] Even where some specific genes are associated with autism, not everyone with those genes develops the condition. Only about 25-50% of those with the Fragile X gene have autistic behaviors that meet the DSM-IV-TR criteria for autistic disorders. Cedillo Tr. at 1485A, 1519. The only gene associated with a near certainty of developing autism is the maternally inherited duplication of chromosome 15q11-q13; a child that inherits this duplicated chromosome will develop an ASD. Cedillo Tr. at 1519-20.

The genetic basis for autism was discovered, just as in most other genetic conditions, through twin studies. A higher concordance rate[134] in monozygotic than in

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[131] DORLAND'S at 1815.

[132] *See* Cedillo Pet. Ex. 117, A. Beaudet, *Autism: highly heritable but not inherited*, NATURE MEDICINE 13(5): 534-36 (2007) ["Beaudet 2007"]. This short article discusses recent studies that indicate de novo genomic deletions and duplications may account for 5-35% of cases of autism.

[133] These causes include tuberous sclerosis, Fragile X syndrome, Rett's disorder, and chromosome 15 anomalies. Cedillo Tr. at 1303A-06A. The distinction between "behavioral symptoms meeting the DSM-IV-TR diagnostic criteria" and being diagnosed with an ASD is a significant one. Because autism is a diagnosis of exclusion, a child with Fragile X syndrome who meets the diagnostic criteria for autism should not be given an autism diagnosis. Cedillo Tr. at 1485A.

[134] "Concordance rate" refers to the percentage of the time that two individuals or groups share the same condition. A 100% concordance rate indicates that the condition is completely controlled by genes. A concordance rate of less than 100% indicates that factors in addition to genes play a role in the development of a condition. DORLAND'S at 404.

dizygotic twins[135] is the hallmark of a genetic disease. Twin studies[136] have demonstrated that, for monozygotic twins, if one twin has autism, there is a 60-70% likelihood that the other twin will also have autism. When developmental abnormalities or language impairments that fall short of a diagnosis of autism are considered in the non-autistic twin, the concordance rate between identical twins rises to approximately 90%. In identical twins, the risk of the second twin having autism is 300 times that of the general population. Cedillo Tr. at 1306A-09.

In fraternal (dizygotic) twins, however, the concordance rate is less than 10%. Siblings of a child with autism have an approximately 25 times greater risk than the general population of being autistic themselves. Expressed differently, siblings of a child with autism have a 5% chance of having autism themselves. Cedillo Tr. 1306A-09A, 1489A-92B; Cedillo Res. Tr. Ex. 10, at 1; Hazlehurst Tr. at 473A-75A.

Because the risk is not 100% that monozygotic twin pairs will both have autism, other factors must play a role in determining who develops the disorder. These other factors account for 8-10% of the risk. Cedillo Tr. at 1494-95. In other diseases or disorders commonly recognized as genetic in nature, the concordance rates between identical twins is much lower than in autism. Cedillo Tr. at 1499-1501, 1514.

One study has determined that 20% of children with an ASD diagnosis have dysmorphic features, an indication of problems in embryonic development.[137] A higher percentage of autistic children with identified genetic abnormalities have dysmorphic features. Cedillo Pet. Ex. 117, at 524 (Beaudet 2007). These two studies suggest a prenatal origin for autism. Although Dr. Kinsbourne testified that children with classic (early onset) autism have more minor congenital anomalies than either typically developing children or children with regressive autism, he did not identify any study that supported this testimony. Cedillo Tr. at 1060-62. If he was referring to the Beaudet 2007 study, it does not support this portion of his testimony. Even if there is a clear link between early onset autistic disorders and genetic anomalies, that link does not preclude a genetic basis for regressive autism as well.

A study of archived cord blood[138] found that more children with either an ASD diagnosis or a diagnosis of mental retardation had abnormal levels of various neuropeptides, as compared to typically developing children. Children with regressive

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[135] Monozygotic, or identical, twins develop from the same fertilized egg. They thus share identical genes. Dizygotic twins develop from different eggs, thus sharing the same genetic risk that other full siblings share of inheriting a genetic condition. DORLAND'S at 1172, 1975.

[136] *See, e.g.*, Bailey, Cedillo Pet. Ex. 61, Tab D.

[137] J. Miles and R. Hillman, *Value of a clinical morphology examination in autism*, AM. J. MED. GENET. 91(4): 245-53 (2000), filed as Cedillo Res. Ex. P, Tab 111.

[138] Cord blood is collected from the umbilical cord at birth. DORLAND'S at 230.

autism had as abnormal a pattern of peptides as did children with ASD without evidence of regression.[139] This strongly suggests the same prenatal origin for both types of autistic disorders and suggests that there are similar brain dysfunctions present at birth in both regressed and classic autism cases. Cedillo Tr. 1318A-22.

Some preliminary work has linked the presence of specific genes and language delay, but there is no consensus on the results. Cedillo Tr. at 2598-99. At present, the knowledge of which genes are involved does not permit ascertainment of specific phenotypes of autism. Cedillo Tr. at 2593A-96.

2. Genetic Expression and Timing of Symptoms.

Citing the lack of a 100% concordance rate in monozygotic twins, Dr. Kinsbourne testified that genetics establish "a susceptibility and not a predestination to autism." Cedillo Tr. at 1051A. However, the geneticist, Dr. Cook, testified that autism is considered a strongly genetic disorder. Cedillo Tr. at 1501, 1510, 1547. The lack of 100% concordance derives from the complexity of the genetic basis for autism and depends on the nature of gene expression (how certain genes turn off, on, or partially on), and on epigenetic[140] influences, all of which play a role in the development of autism and the nature and severity of its symptoms. Cedillo Tr. at 1499-1505, 1552A-53; *see also* Hazlehurst Tr. at 474A-75A. Doctor Rust explained that patterns of brain development at particular times explain both the timing and nature of many of autism's symptoms, including the apparent loss of skills. Hazlehurst Tr. at 466A, 536A-37A. *See also* Bailey, Cedillo Pet. Ex. 61, Tab D, at 74.

Although autism may not manifest itself until the second year of life, that timing does not require a contemporaneous triggering event. In many genetic disorders, the risk of the disorder is present at birth, but the symptoms do not manifest until a later time. Rett's disorder, a condition with many parallels to autism, involves apparently normal development, followed by a regression of skills. This is a wholly genetic disorder. There is no triggering event, simply a point in time when the MECP2 gene that causes Rett's disorder is expressed and the defects in that gene result in the manifestation of various symptoms. Cedillo Tr. 1495-98, 1500. Huntington's chorea is a disorder controlled by one dominant gene, present at conception, but silent for decades. When the gene "turns on," the symptoms manifest. An individual with the

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[139] K. Nelson, *et al., Neuropeptides and Neurotrophins in Neonatal Blood of Children with Autism or Mental Retardation.* ANN. NEUROL. 49(5): 597-606 (2001), filed as Cedillo Res. Ex. P, Tab 115.

[140] Epigenetics are influences that affect gene expressions. Hazlehurst Tr. at 463A-64A. The term may pertain to nongenetic causes of disease. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 433; DORLAND'S at 627. Doctor Kinsbourne analogized the role of genes and epigenetic factors to a commanding officer giving orders to his unit to get to a certain place. How the individual soldiers arrive (or fail to arrive) is influenced by terrain, pathways, and roadblocks. The gene expression is the order; the outside factors that influence if, how, and when the troops arrive are the epigenetic influences. Snyder Tr. at 478A-79A.

gene is asymptomatic at age 20, but by age 70, the person is certain to have symptoms. Cedillo Tr. at 1499. *See also* K. Nelson and M. Bauman, *Thimerosal and Autism?* PEDIATRICS, 111: 674-79 (2003) ["Nelson and Bauman 2003"], filed as Cedillo Res. Ex. L, Tab 43, at 675 ("If we did not understand its genetic basis, we might suspect that Rett Syndrome was attributable to environmental factors including immunization. The situation for autism is still unknown, but the onset of signs in the second year of life does not prove (nor disprove) a role for environmental factors in etiology.").

Doctor Zimmerman's report reflected his concurrence with the position that the manifestation of autism is not the result of an external environmental trigger. He stated that the appearance of autism in the second and third years of life "reflects the dynamic nature of the child's developing brain and the appearance of pre-programmed disordered expression of genes and pre-existing cellular abnormalities that result in the child's regression with loss of language and social skills." Cedillo Res. Ex. FF at 3.

Gene expression can be analogized to traffic lights. When the light turns green, the gene is fully expressed. When the light is yellow, the gene is only partially active. When the light is red, the gene is not active at all. To continue the analogy, the change in the traffic signal from red to green or yellow, depends on how the light is constructed, as well as on events outside the light that affect its function. Traffic lights may change based on elapsed time, traffic volume, speed of approaching cars, or even by the time of day. These "traffic signaling" devices may be internal to the gene or caused by epigenetic influences. Cedillo Res. Ex. N at 2; Cedillo Tr. at 1499-1501; 1552A-53.

Gene expressions have similar triggers, such as stages of development or age. Just as a timer may trigger the change in a traffic light from red to green, the Huntington's gene or the Rett's gene may be triggered by elapsed time. Cedillo Tr. at 1552A-53; 1495-98. Other conditions with a genetic basis also have specific times for manifestation. For example, infantile spasms manifest at four to six months of age. Hazlehurst Tr. at 513A.

As the brain develops from infancy to adulthood, some centers of brain activity go off-line and the functions they controlled are shifted to other centers. Doctor Rust illustrated the activity centers of the maturing brain through a series of photographs reflecting the cortical development of the brain. Hazlehurst Res. Tr. Ex. 1 at 13. During infancy, brain cells migrate from deep in the brain to the outer portion of the brain to form the cortex. Cortical cells communicate through a complex system of fiber pathways or connections between layers of the cortex, as well as with other areas of the cortex. As the cortex forms, there is an increase in its activity level, and brain activities that were controlled by the deeper brain centers switch to the control of the new cortical centers. Hazlehurst Tr. at 457A-62A. This migration, and the establishment of the communication networks between various areas of the brain, is influenced by genes and by epigenetic factors, which may include environmental influences. Hazlehurst Tr. at 462A-63A. Migrating brain cells may help to turn on or off

the expression of a particular gene. Cedillo Tr. at 1552-54.

Doctor Rust provided an illustration of the impact of a prenatal brain insult that would not manifest for months after birth. He explained that an infant who experienced a prenatal stroke involving both hemispheres of the brain could appear perfectly normal until two and a half or three months of age. At that time, certain brain activities switch from the deeper centers to the cortical centers as the result of genetic programming, and symptoms of the stroke first manifest when the infant is unable to display developmentally expected behaviors. Hazlehurst Tr. at 457A-59B.

There are several phases of brain maturation during the first 18 months of life. These are tied to developmental milestones, such as social smiling, sitting, and the development of language. Cedillo Tr. at 1498-99. Because brains are not rigidly constructed, environmental factors undoubtedly affect brain development and the display of these milestones. Many brain structures present at birth are modified during early development, while others form new connections. After birth, some brain cells are still in the process of migrating from deep in the brain to the higher cortical areas. Random factors affect this developmental process. Cedillo Tr. at 1494-95; Hazlehurst Tr. at 461A.

In a child with a genetic vulnerability or risk for autism, brain cell migration may modify or exacerbate the genetic vulnerability. These events may not be what people customarily think of as environmental, but when scientists talk about environmental risk factors in autism, these are the risk factors they are referencing. Most environmental risks for autism are prenatal. Cedillo Tr. at 1494-95. *See also* Cedillo Res. Ex. FF at 3. In this report, Dr. Zimmerman indicated that the primary environmental factor in immune research in autism is the mother's immune system and its effects on the developing fetus). *See also* IOM 2004 Report, Cedillo Res. Ex. JJ, at 33-34 ("The consensus of most scientific experts is that autism is generally caused by early prenatal exposures...or is linked to early developmental genes.").

Symptoms of regression are often noted during the period between 12-27 months of age, although many of these children had earlier manifestations of abnormal development. During this period of development, additional genetically-programmed switching takes place. Hazlehurst Tr. at 460A-62A. Doctor Rust described the regression as resulting from "replacement of more primitive systems of wiring with more sophisticated systems of wiring and some things going offline." Hazlehurst Tr. at 472A.

There are other periods of brain development when abnormalities may manifest. Girls with Rett's disorder have an additional period of deterioration between five to six years of age. Many autistic children have additional deterioration during their teen years. Hazlehurst Tr. at 462A.

The evidence presented on genetics and gene expression tends to undercut petitioners' arguments that regressive autism is likely to have a cause distinct from that

of classic or early onset autistic disorders. Thus far, there is no evidence at all that regressive autism has a genetic basis separate from classic or early onset autistic disorders. A difference in timing does not, *ipso facto*, constitute a different genetic cause.

3. Pathophysiology of Autistic Brains.

Some body organs appear to have only one primary function. The lungs, for example, oxygenate the blood, and the specific action of the left upper lobe does not markedly differ from that of the right lower lobe. In contrast, the brain is comprised of sections that have very different functions and which vary in the degree and nature of their interactions with each other. The infant brain differs dramatically from the adult brain, as Dr. Rust's brain development slides illustrated. Hazlehurst Res. Tr. Ex. 1 at 13.

On external macroscopic examination, the brains of autistic children show no obvious abnormalities. On microscopic evaluation of brain tissue, however, significant differences are found in the brains of autistic children as compared to aged-matched controls. Cedillo Tr. at 1310-11A. Brain pathophysiology in autism has primarily been established through autopsy of adult brains, not children, but functional magnetic resonance imaging ["MRI"] studies can help correlate findings from autopsies to the same areas of the brain in younger individuals. Based on what is known about brain development, scientists can determine when the dysgenesis[141] began. In terms of cortical development, the time frames at which various developmental processes occur is clearly established. Hazlehurst Tr. at 535A-36A.

The number of neurons in the brain does not change much between birth and adulthood. Snyder Tr. at 477A. Early in development, the connections between the neurons are primarily local. As myelination occurs, the axons can transmit information more quickly and over longer distances. Snyder Tr. at 478A. Although a gene may tell the neurons to line up at a particular place, epigenetic influences affect how the neurons get to the prescribed locations, whether they arrive slightly out of place, or fail to arrive at all. Snyder Tr. at 478A-79A. The brain is dynamic, not static. Snyder Tr. at 479A.

Specific changes have been observed in comparisons of brain structure in autistic individuals, as compared to typically developing controls. Purkinje cells, found in the cerebellum, are absent or found in decreased numbers in autistic brains. The mini-columnar structure is abnormal, and the brain cortex is thickened. The amygdala connections with the forebrain, the cortex, and the minicolumns are abnormal. Snyder Tr. at 546A-47A (Dr. Kinsbourne concurring that all three areas are abnormal on autopsy).

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[141] "Dysgenesis" is defective development. DORLAND'S at 574.

Purkinje cells receive connections through climbing fiber axons from neurons located in a part of the brainstem called the inferior olive. This connection between the brainstem and the Purkinje cells is established, at the latest, by 30 weeks of gestation. If a Purkinje cell is destroyed after this connection is established, retrograde cell loss affects the climbing fiber axons. In studies of autistic brains, the Purkinje cells are absent, but the climbing fiber axons are present. This indicates that the Purkinje cells actually formed, but were lost early in gestation, before the connection was established. Otherwise, the climbing fiber axons would be missing. Cedillo Tr. at 1088-89A, 1310-13A. *See also* T. Kemper and M. Bauman, *Neuropathology of Infantile Autism*, J. NEUROPATH. AND EXP. NEUROLOGY 57(7): 645-52 (1998), filed as Snyder Res. Ex. Y, Tab 6, and M. Bauman and T. Kemper, *Neuroatomic observations of the brains in autism: a review and future directions*, INT'L. J. DEVL. NEUROSCIENCE, 23: 183-87 (2005) at 185, filed as Cedillo Pet. Ex. 61, Tab I.

Doctor Rust explained that the critical pathological change in the brain of autistics is in the amygdala, a deep brain structure that is part of the limbic system. The amygdala connects with the forebrain, the cortex, and the minicolumns. Hazlehurst Tr. at 480A-83A. *See also* R. Muller, *The Study of Autism as a Distributed Disorder*, MENTAL RETARD. DEV. DISABILITIES RES. REV. 13: 85-95 (2007), filed as Hazlehurst Res. Ex. G, Tab 24.

The organization of the grey matter in the cortex of the brain is also impaired. Grey matter cells in normal brains are arranged in very orderly columns at right angles to the surface, but in autistic brains, the columns are disorganized. Cedillo Tr. at 1088-89A.

The total number of minicolumns is determined in the first 40 days of gestation. Cedillo Res. Ex. P at 21. The minicolumns connect laterally and to other parts of the brain. In autism, the minicolumnular structures are abnormal and the cortex above them is thickened. Hazlehurst Tr. at 480A-83A. The dysgenic changes in minicolumns occur early in childhood.[142] Other changes in the brains of autistic individuals must have taken place intrauterinely. Hazlehurst Tr. at 536A.

Numerous studies have found that many, although not all, autistic children have head circumference measurements different from those that are typical for their age and sex. About 20% of autistic children have macrocephaly,[143] which, in infants and toddlers, is indicative of abnormal brain growth. At birth, the mean head circumference of autistic children is normal, but by three to five months of age, head growth is

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[142] Doctor Rust's testimony about minicolumn differences in autistic brains is supported by the research of Dr. M. Casanova. *See, e.g.*, M. Casanova, *et al., Minicolumnar pathology in autism*. NEUROLOGY 58(3): 428-32 (2002), filed as Cedillo Res. Ex. P, Tab 20. This exhibit is one of several articles by Dr. Casanova on brain pathology in ASD.

[143] Macrocephaly is defined as a head circumference larger than 97% of the population of a specific age and sex. Cedillo Tr. at 1314A-15.

accelerated. By six to fourteen months of age, the mean head circumference of many autistic children is significantly greater than the norm. By two to four years of age, the accelerated head growth has ceased. A plateau is reached around the time behavioral symptoms of autism emerge. Cedillo Tr. at 1314A-17A; *see also* Cedillo Res. Ex. DD, Tab 4.[144] Even when the relationship between height and head circumference is considered, autistic children have, on average, larger head circumference than non-autistic children. Cedillo Res. Ex. P, Tab 101;[145] Cedillo Tr. at 1457A-59A.

MRI studies have documented enlarged white matter in the cerebellum of autistic children, but the studies are not consistent in finding enlargement in specific areas. Cedillo Tr. 1317A-18A. In younger autistic children, neuroimaging demonstrates an increased amount of white matter, particularly in the area behind the frontal lobe. There is no consensus on what causes the enlarged areas of white matter. Cedillo Tr. at 1089A.

The specific brain structure abnormalities seen in autism are distinct. They occur in highly select areas of the brain, and particularly in the evolutionarily advanced areas of brain architecture. Hazlehurst Tr. at 486A. The structural abnormalities seen in autism are not the same as those seen after toxic exposures, encephalitis, or other acquired brain injuries. They have their basis in a developmental process. Hazlehurst Tr. at 488A. Neither a toxic event nor an inflammatory one can produce the combination of changes seen in autistic brains. Hazlehurst Tr. at 495A-96A.

These neuropathologic findings, coupled with the association of autism with certain prenatal exposures, strongly indicate that autism has a prenatal onset. The evidence for autism's genetic basis and prenatal origin renders petitioners' MMR theory of causation improbable, as a vaccination in the second year of life is unlikely to generate the brain structure changes seen in ASD. Petitioners have not demonstrated that their postulated regressive autism phenotype is etiologically distinct from other forms of ASD.

Section V. Immunology and TCVs.

A. Introduction to the Immune System.

Virtually all the evidence presented in the Theory 1 cases involved complex scientific concepts, but the evidence pertaining to the purported effects of the MMR vaccine and TCVs on the immune system was the most complex of all. It cannot be understood without a basic knowledge of how the immune system works.

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[144] G. Dawson, *et al., Rate of Head Growth Decelerates and Symptoms Worsen in the Second Year of Life in Autism,* BIOL. PSYCHIATRY 61: 458-64 (2007).

[145] J. Lainhart, et al., *Head circumference and height in autism: a study by the Collaborative Program of Excellence in Autism*, AM. J. MED. GENET. 140(21): 2257-74 (2006).

Unfortunately, much of the testimony of petitioners' immunology expert, Dr. Byers, tended more to obfuscate than elucidate. Doctor Kennedy's testimony was much clearer and more reliable than that of Dr. Byers. His experience and training qualified him to testify about the immune system in general. However, because he does not have a medical degree, clinical expertise in caring for humans, or experience running a clinical laboratory, he was less qualified than Dr. McCusker or Dr. Ward to explain the significance of test results and the functioning of the human immune system.

I found Dr. McCusker, respondent's immunologist, to be an excellent expert witness. She carefully explained difficult concepts, appropriately qualified her testimony, and her credibility was enhanced by her years of experience in diagnosing and treating immune system problems in both typically developing children and those with autism. Doctor Ward's testimony was careful, reasoned, and well-supported by medical literature and his own experience. For basic concepts not otherwise explained by the experts, I relied upon *How the Immune System Works* by Lauren Sompayrac (2d ed., Blackwell Publishing) (2003). There do not appear to be any genuine issues of fact in this section before reaching the issue of immune system "skewing" in Part A.2.c.(3), below.

The human immune response to pathogens is mounted by the innate and adaptive immune systems. These two systems fight pathogens in different and complementary ways. Like the Army and Air Force, they bring different types of combat power to the battle, and they each function optimally when they communicate well. The innate immune system is the first responder. When the innate immune system calls for help, the adaptive immune system is activated and deployed, taking about four to seven days before it enters the battle. Cedillo Tr. at 689A-90B.

The components of the two systems are a veritable alphabet soup of cell types, receptors, and signaling mechanisms. For that reason, Appendix A to this opinion contains a glossary of terms.

1. Innate Immune System.

The innate immune system provides a rapid, but non-specific, response to the presence of pathogens. In addition to natural barriers to infection, including skin and mucous, the innate immune system relies on specialized white blood cells, called phagocytes, complement proteins (which were discussed only in passing in the testimony and exhibits), dendritic cells ["DC"], and natural killer ["NK"] cells (a type of lymphocyte) to act as the body's initial defense against invaders. Cedillo Tr. at 691, 697A, 2772A; Cedillo Res. Ex. R at 2. The innate immune system also produces

cytokines,[146] and is largely responsible for inflammation and fever. Cedillo Tr. at 691, 2772A. The innate immune system cells can communicate the presence of the invading pathogen to the adaptive immune system, kick-starting its reaction. Cedillo Tr. at 691-95, 697-98; Cedillo Pet. Tr. Ex. 8 at 5.

a. Phagocytes.

Phagocytes are cells that engulf or ingest microorganisms or particles in a process called "phagocytosis." They include macrophages and neutrophils.

In tissue, macrophages act like vacuum cleaners, cleaning up cellular debris. When they encounter an invading pathogen, they engulf or ingest it, breaking it up into peptides. Snyder Tr. at 575A. In the process, they produce cytokines. The cytokines alert other macrophages that an invader is present. Macrophages that receive such signals are said to be "activated" or "primed." Once activated, they can function as antigen presenting cells ["APCs"] that communicate the nature of the invading pathogen to the adaptive immune system. One cytokine known to activate macrophages is interferon gamma ["IFN-γ"], which is produced by helper T cells and NK cells. Cedillo Res. Ex. R at 2.

Macrophages can become hyperactivated by direct signals from invading pathogens, such as lipopolysaccharides[147] ["LPS"]. When hyperactivated, the macrophage grows larger and focuses on killing invaders. Hyperactivated macrophages produce the cytokine known as tumor necrosis factor ["TNF"], which can kill tumor cells and virus-infected cells, and can activate other components of the immune system. The release of cytokines produces inflammation.

Neutrophils make up about 70% of the white blood cells in circulation. They

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[146] Cytokines are hormone-like proteins that communicate between immune system cells. In essence, they are messages or orders sent from one cell to another. Some act locally; others act over distances. Some cytokines are classed as interleukins ["IL"]; the different types of interleukins are assigned numbers to distinguish them. Interleukins that are assigned low numbers (i.e., IL-1 and IL-2) and some other cytokines, such as tumor necrosis factor ["TNF"], that are assigned no number, are produced in very large quantities in the body and are not well regulated. These are produced quickly and elicit proinflammatory responses. For instance, IL-1 produces a high fever when injected. Cedillo Tr. at 1813A-15. The more recently discovered cytokines, generally the ones assigned higher numbers, are more tightly regulated, do more specific things within the body, and are produced in much smaller quantities. Cedillo Tr. at 917-18, 1812A-13A, 2235A-39. Cytokines can be classified several different ways: as proinflammatory and anti-inflammatory or as those that act over short distances or over long distances. Most act over only short distances, particularly those that are responsible for activating cellular responses. Cedillo Tr. at 2236. Those that act over long distances tend to be more proinflammatory, such as IL-1. Cedillo Tr. at 1897-98, 2237-39. Cytokines are involved in all immune responses. They are also used in the central nervous system ["CNS"] to communicate between leukocytes and glial cells. Cedillo Tr. at 2236-37.

[147] Lipopolysaccharides are molecules contained in the cell walls of many bacteria. Cedillo Tr. at 1006.

have a very short life span, about five days, after which they die by apoptosis.[148] Cedillo Tr. at 895.

Dendritic cells are probably the most important class of APCs. They are located at places where pathogens may invade the body, including the skin, the lining of the lungs and gut, and in the liver. In their resting state, they act as phagocytes, engulfing and digesting infected cells and viruses. Cedillo Res. Ex. R at 2. However, when toll-like receptors ["TLR"] on the surface of dendritic cells recognize LPS or cytokines (such as TNF) that indicate a pathogenic invasion, they become activated. Upon activation, they travel from the tissue through the lymphatic system to nearby lymph nodes. They display antigens, fragments of proteins from viruses or other parasites, on their cell surfaces, and activate T cells in the lymph nodes. Cedillo Tr. at 692-97A, 906B-09A, 2231A-33A; Cedillo Res. Tr. Ex. 16, at 11. APCs assist the adaptive immune system to recognize and respond to invading pathogens. Cedillo Tr. at 696-97A.

b. Natural Killer Cells.

Natural killer cells, as their name implies, are versatile killers, capable of killing tumor cells, virus infected cells, bacteria, parasites, and fungi. They kill cells by "injecting" them with compounds that trigger cell death or by binding to the surface of the target and sending chemical signals that induce cell death. Like macrophages, they are more effective killers when activated by chemicals such as LPS or when they receive interferon alpha ["IFN-α"] or interferon beta ["IFN-β"] given off by cells attacked by viruses.

c. Response to Viruses.

Viruses reproduce by hijacking a cell's machinery to produce more copies of the virus. Those copies exit the cells and infect neighboring cells. When viruses are in transit between cells, the innate immune system can recognize and destroy them, but the innate immune system is much less effective against viruses inside cells. The innate immune system is excellent, however, at signaling the adaptive immune system about the viral invasion. Cedillo Tr. at 2231A-33A.

2. The Adaptive Immune System.

As its name implies, the adaptive immune system can adapt to fight almost any invading pathogen. Although it requires time to recognize a new invader, and to recruit and equip the army to fight it, once it encounters and defeats a specific pathogen, it can respond quickly to future invasions. Because the cells that were most effective against the pathogen become part of the adaptive immune system's memory, the adaptive immune system can mount a more rapid and tailored response to subsequent attacks.

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[148] Apoptosis is programmed cell death. DORLAND'S at 117. In essence, the cell has a natural lifespan, at the end of which it self-destructs.

The primary components of the adaptive immune system are B and T lymphocytes. B cells mature in the bone marrow; T cells mature in the thymus. Cedillo Res. Ex. R at 2. Once mature, both B and T cells enter the blood stream and circulate between the circulatory and lymphatic systems.

Like the innate immune system, the adaptive immune system also uses cytokines to communicate and mount a response. Cedillo Tr. at 692. Antigen recognition molecules found on the surface of the cellular components of the innate immune system are key to the system's ability to recognize and respond to invaders. Cedillo Tr. at 692-93.

The adaptive immune system has two arms, the humoral arm and the cell-mediated arm. The humoral arm of the adaptive immune system consists of B cells and CD4 T cells.[149] The cell-mediated arm, consisting of CD8 T cells, is focused on killing intracellular pathogens. Cedillo Tr. at 701-02. These cell types are explained in more detail below.

a. B Cells.

B cells are produced daily in the bone marrow and mature there. While there, these naive B cells[150] "select" the two proteins that become B cell receptors on the cell's outside surface. Through a mix and match process of selecting proteins for their receptors, a B cell can be made that recognizes almost any organic molecule, although an individual B cell can recognize only its specific "cognate"[151] antigen. Antigen recognition activates B cells to produce antibodies. Snyder Tr. at 576A. Antibodies are the functional molecules in B cells. Antibodies are serum proteins and are generally referred to as immunoglobulins. Cedillo Tr. at 698-99.

To activate naive B cells, a co-stimulation may be necessary, and is usually provided by a helper T ["Th"] cell. Some antigens, particularly those on the surface of many bacterial cells, can activate a naive B cell without T cell assistance. Activated and proliferating B cells enter the maturation stage, which consists of "class

[149] Some of the slides and medical journal articles filed alternatively identify these cells as CD4+ T cells. The terms are synonymous. CD8 T cells are likewise alternatively identified as CD8+ T cells. DORLAND'S at 1077.

[150] A naive B cell is one that has not yet encountered the antigen it is capable of recognizing. DORLAND'S at 318, 324. An antigen is a protein expressed on the surface of a pathogen. DORLAND'S at 103.

[151] "Cognate" is defined as of the same or similar nature. THE MERRIAM-WEBSTER DICTIONARY at 96 (6th ed. 2005).

switching,"[152] "affinity maturation,"[153] and a choice between manufacturing antibodies or becoming a memory cell.

New B cells display immunoglobulin M ["IgM"] on their cellular surfaces. Once activated in response to its cognate antigen, the B cell is able to mass produce IgM antibodies. B cells may also switch the class of antibodies they produce from IgM, to IgG, IgA, or IgE. Cedillo Tr. at 699-700.

IgM antibodies bind to the surface of invaders in a process called "opsonizing,"[154] and can signal parts of the innate immune system to attack those invaders. IgM antibodies can bind to the surface of viruses and prevent them from infecting cells. Antibodies are generally ineffective against viruses that have entered cells. Cedillo Tr. at 2764-67.

IgG antibodies, also known as gamma globulins, exist in four types, or subclasses, each with different functions, although each subclass is able to opsonize, or tag, invaders to trigger phagocytosis and each is able to neutralize some viruses in transit between cells. Cedillo Tr. at 700-01. IgG antibodies pass from mother to fetus through the placenta, providing antibody protection for the newborn until it begins to produce its own antibodies. Cedillo Tr. at 699-700. An individual who is deficient in one subclass of IgG may be more prone to certain infections. Cedillo Tr. at 701.

IgA antibodies protect the body's mucosal surfaces. Snyder Tr. at 587A. They can enter the intestines from the bloodstream and blanket invading pathogens before the pathogens can attach to cells. Cedillo Pet. Tr. Ex. 8 at 6.

Antigens that can cause allergic reactions are called allergens. Upon first exposure to an allergen, some individuals manufacture large quantities of IgE antibodies directed against that allergen. Cedillo Pet. Tr. Ex. 8 at 6.

b. T Cells.

There are several classes of T lymphocytes. Upon activation, one class of T cells becomes cytotoxic. These killer T cells do what their name implies–kill cells infected with viruses. Cedillo Tr. at 883A-34A. The other class of T cells is the Th cells. Th cells activate other cells, including B cells and macrophages. They induce B

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[152] Class switch is the method by which a B cell changes from production of IgM to IgG, IgA, or IgE antibodies. DORLAND'S at 1803.

[153] Affinity maturation selects, over a period of months, the cells with the highest affinity for the measles antigen. In most diseases, this confers life-long immunity after an initial infection. Cedillo Tr. 2764-67.

[154] Opsonization involves tagging invaders to identify them to other immune system components that can destroy them. DORLAND'S at 1319.

cells to produce antibodies. Cedillo Tr. at 1002A. T regulatory cells help direct the type of immune response required and calm immune system reactions after a pathogen has been defeated.

Both cytotoxic and helper T cells contain receptors on their surface that recognize only certain antigens. Cedillo Res. Ex. R at 2. T cells that have not encountered their cognate antigen are called “naive” T cells. Cedillo Tr. at 695-97A, 2763-64. Prior to maturation, T cells have both CD4+ and CD8+ receptors. As they mature, one receptor is selected. Killer T cells have CD8+ receptors; Th cells have CD4+ receptors. Cedillo Res. Ex. R at 2.

Helper T cells are activated in the lymph nodes by DC. Snyder Tr. at 575A-76A. Once a T cell is activated, it proliferates, stimulated by IL-2, which is produced by activated B cells. After proliferation, Th cells mature into effector T cells. Effector T cells assist B and cytotoxic T cells and other cellular components of the innate and adaptive immune systems. Some remain in the blood and lymphatic system and some exit the circulatory system at locations where pathogens are being fought. Cedillo Tr. at 695-97A, Cedillo Tr. at 1002A.

c. Th Responses.

In addition to activating naive T cells, DC inform them what type of response would be best to counter the threat. Based on this information, effector T cells become Th1, Th2, or T regulatory [“T Reg”] cells, based on the type of cytokines they begin to express. The cytokines secreted generally fall into one of two categories (Th1 or Th2), although some Th cells secrete both categories of cytokines (Th0 cells). Effector T cells that encounter activated macrophages secreting IL-12 will develop a Th1 profile; those that encounter a parasitic invasion receive IL-4 cytokines, and develop a Th2 profile, meaning that they secrete cytokines of the Th2 type. Cedillo Tr. at 2231A-33A; Cedillo Res. Tr. Ex. 16, at 11. Effector T cells that develop one profile also help convert other effector T cells to develop the same profile and encourage the proliferation of cells biased toward their Th profile.

The types of cytokines secreted, Th1 or Th2, help develop an immune response tailored to the nature of the invading pathogen. Generally speaking, the tailored response is local, rather than systemic. That is, Th cells that secrete one type of cytokine may predominate in one part of the body, but many Th cells that secrete the other type remain active throughout the body. Cedillo Tr. at 2235A-39.

(1) Th1 Response.

Cytokines identified as part of a Th1 response, include IL-2, IFN-γ, and TNF. A Th1 response helps the body defend against viral or bacterial attacks in blood and tissue and is, simplistically, viewed as cellular immunity. Cedillo Tr. at 700-04, 1876A-77A. Th1 cells assist CD8+ cells to become cytotoxic T cells. Cedillo Tr. at 701-02.

(2) Th2 Response.

The Th cells that produce a Th2 response generate IL-4 and IL-5 cytokines. IL-4 can also induce a class switch in B cells to IgE, and cause increased production of IgG1, IgG3, and IgG4. Cedillo Tr. at 2230A. IL-5 induces a class switch to IgA antibodies. Thus, a Th2 response is useful against parasitic or mucosal infections. Simplistically, a Th2 response is viewed as an antibody response. Cedillo Tr. at 703-04, 1877.

(3) Th1/Th2 "Skewing."

Doctor McCusker explained the development of theories surrounding Th1 and Th2 "skewing." The 1986 discovery[155] that some T cells produced IFN-γ, while others produced IL-4, resulted in the labels "Th1" and "Th2" being assigned to the IFN-γ and IL-4 producing T cells, respectively. These two cytokines work in balance to direct immune response. Cedillo Tr. at 1807-08. Because IFN-γ was important for macrophage activation, as well as for cell mediated immune response, the Th1 immune response was considered to be cell mediated. Because IL-4 was important for the activation of B cells and, thus, the formation of antibodies, Th2 was considered to be the humoral arm of the immune system. Cedillo Tr. at 2225A-27A. However, the theory of Th1/Th2 skewing has flaws. Th1 and Th2 responses were defined in inbred mice, which have a simpler immune system than humans do. The concept of immune balance is relatively new and the term generally refers to a predominance of Th1 or Th2, rather than the complete lack of one form of response. In humans, unlike mice, Th1 responses do not necessarily suppress Th2 responses, or vice versa. Cedillo Tr. 1807A-08, 1810-11A, 2227A, 2229A.

Another type of T cell, the T regulatory cell, begins to increase as the threat level declines. When the threat from the pathogen is high, Th1 or Th2 cells respond by activating cytotoxic T cells and antibody producing B cells. T regulatory cells calm down the immune response. Cedillo Tr. at 2228A-30A.

Immune balance is a dynamic system, strongly influenced by genetics. Some human populations have predispositions toward Th1 or Th2 responses. Children with asthma and allergies tend toward a humoral bias. Cedillo Tr. at 1811A-12A. Someone with Th2 skewing would be in the 30% of the population with allergies, as a Th2 bias is characterized by excess IgE production. Cedillo Tr. at 2239-40. The balance can change from day to day, and even from location to location, within the body. Stress and fatigue cause shifts in immune balance that correct with relaxation and rest. Cedillo Tr. at 1811A.

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[155] *See* T. Mosmann*, et al., Two Types of Murine Helper T Cell Clone.* J. IMMUNOL. 136(7): 2348-57 (1986), filed as Cedillo Res. Ex. Z, Tab 12.

3. Immune System of the Brain.

For its adaptive immune response, the brain relies on the same adaptive immune system found in the rest of the body as part of its protection against invading pathogens. The lymphocytes circulating in the blood are the same lymphocytes found in the CSF. Snyder Tr. at 950-51A. However, the brain has its own innate immune system, consisting of microglial cells. When these cells encounter a pathogen or a cytokine signaling the presence of a pathogen, they become activated. Cedillo Tr. at 1075A, 1091-92A. Microglial activation may also occur as the result of breakdown (destruction) of neuronal cells, whether in response to pathogens or as the result of some other process. Cedillo Tr. at 1091.

B. Immune System Malfunctions.

Immunodeficiency, immune dysfunction, and immune dysregulation are terms used to describe malfunctions in the immune system. Cedillo Tr. at 707A. Immune system malfunctions may be primary (congenital) or secondary (acquired). These defects can affect the innate or adaptive immune systems, or perhaps both. Cedillo Tr. at 1803A-04.

The witnesses disagreed over the meanings of the terms they used in discussing immune system malfunctions. Doctor Kennedy defined "immune dysfunction" as an umbrella term encompassing problems associated with the normal functioning of the immune system. Cedillo Tr. at 735A. In contrast, Dr. Ward testified that the terms "immune suppression," "immune defects," and "unbalanced" or "dysregulated" immune response have very specific meanings and cannot be used interchangeably. Cedillo Tr. at 1801A-02. Doctors McCusker and Zweiman also disagreed with Dr. Kennedy about the use of the term "immune dysregulation." Doctor McCusker disparaged the use of the term "immune dysfunction," calling it "one of those very nebulous terms that is used when you cannot make a definition of anything." Cedillo Tr. at 2262-63. Doctor Zweiman provided similar testimony. Snyder Tr. at 589A.

According to Dr. McCusker, the pediatric immunology community does not use the term "selected immune dysfunction." She explained that the term "immune abnormality" would be used when there is evidence of an objective laboratory abnormality. "Immune deficient" would bring together the objective laboratory finding with evidence of a clinical abnormality. Cedillo Tr. at 2263, 2289. Doctor Zweiman explained than an individual can be immunodeficient but that does not mean that the person has an immune dysregulation. Snyder Tr. at 589A-90A.

There was general agreement that immune system malfunctions–however they are characterized–can have a genetic component or can be acquired.

1. Primary Immune System Defects.

The term “immune defects” refers to primary immune system problems–genetic defects in the immune system. These defects can involve the innate or adaptive immune systems or they can involve defects in both. Cedillo Tr. at 1803A. Primary immunodeficiency is an inherited (genetic) disorder affecting approximately 1 in 500 individuals in the U.S. Cedillo Tr. at 707A-08. Severe combined immunodeficiency syndrome [“SCID”] is perhaps the best known form of primary immune deficiency, and can be severe enough to require children to live in a germ free, or “bubble,” environment. Cedillo Tr. at 707A, 1803A. Children with SCID present with severe infections within the first year of life and die without medical intervention. Hazlehurst Tr. at 584A.

Common variable immunodeficiency is a less severe form of immunodeficiency. Individuals with this disease have defects in some aspects of their immune system that affect their bodies’ ability to deal with specific types of infections. Cedillo Tr. at 707A-08. For example, an individual may be defective in one IgG subclass. If vaccinated against a disease, the individual may respond to the vaccine robustly, but still acquire the disease. Cedillo Tr. at 708-09. Immune defects are rarely pathogen specific. Instead, they render an individual vulnerable to a range of similar organisms. Cedillo Tr. at 1803A-04.

Children with more subtle immunodeficiencies may initially appear normal, but they become progressively more ill over time, because their immune systems are overwhelmed with the quantity of pathogens to which they are exposed. Within the first two or three years of life, it would be common for a child with this type of defect to experience several bouts of pneumonia or other recurrent infections. Hazlehurst Tr. at 584A; Cedillo Tr. at 2239-40.

Immune deficiencies are not the same thing as autoimmune disease (autoimmunity). Snyder Tr. at 587A. Children with autoimmune disease have abnormally functioning immune systems, but they are not considered to be immune suppressed or immune deficient. Cedillo Tr. at 1817. Immunosuppression is a significant medical status. Cedillo Tr. at 1802. A predominantly Th2 response is not indicative of immunosuppression. Cedillo Tr. at 2239-40.

2. Secondary Immune System Defects.

Secondary, or acquired, immune system malfunctions may result from environmental causes. Malnutrition can trigger immune system problems, as can heavy metal exposure (which includes mercury), viruses (such as HIV and human T cell

leukemia virus 1),[156] chronic malaria infection, cancer, chemotherapy, radiation, trauma, burns, and certain drugs. Cedillo Tr. at 706, 709-10. Age may also affect immune status, with the very young and the very old having less robust immune systems. Cedillo Tr. at 711A.

3. Indicators of Immune System Malfunctions.

Significant disagreements developed among the witnesses over what clinical indications reflect immune system malfunctions and the significance of deviations from developed norms. On the whole, I found the testimony of Drs. McCusker and Ward far more persuasive and reliable than that of Drs. Byers and Kennedy.[157]

Doctor McCusker's greater experience in clinical medicine and pediatrics, including her experience in operating a laboratory, gave her testimony considerable weight. Doctor Ward runs a reference laboratory and has extensive experience in vaccine immunology. Cedillo Tr. at 1797, 1799. Their opinions were more often supported by relevant medical literature. Cedillo Tr. at 2211-13.

Unlike Drs. Byers and Kennedy, Dr. McCusker actually sees and diagnoses pediatric patients with immune system problems. Dr. Kennedy is not a medical doctor and his area of expertise is not in human patients.

a. Evaluation of Possible Immune Problems.

(1) History of Illnesses.

In evaluating a patient for immune system problems, a clinician begins with a family and personal history. A history of frequent or unusual infections in a child would be compared against the CDC criteria for the usual number of infections expected in children of comparable age.[158] Infections for which antibiotics are prescribed are of particular interest. Unusual reactions to vaccines and chronic inflammatory conditions are other facts that might suggest immune system problems. Cedillo Tr. at 873A.

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[156] Although Dr. Kennedy testified that the measles vaccine virus can cause immune suppression or immunodeficiency, his statement was challenged by several other witnesses with greater expertise regarding measles virus. Cedillo Tr. at 710, 1887A. I address the issue of the immunosuppressive effects of measles virus elsewhere in this opinion.

[157] During the testimony in *Snyder*, it became apparent that much of Dr. Kennedy's testimony about the measles virus came from Dr. Griffin's chapter in Field's Virology. *See* Snyder Tr. at 1000-04A. However, he relied upon an outdated version of that reference. Snyder Tr. at 1004A. In surrebuttal, Dr. Rima noted that information known to be outdated or incorrect by those in the field of measles virology may appear in textbooks. Snyder Tr. at 1007A-08A. This is more likely when the textbook in question has been superceded by a new edition.

[158] Between six months and two to three years of age, the average child has six to 10 infections per year. Hazlehurst Tr. at 568A.

(2) Types of Testing.

The focus of immune testing is on the adaptive immune system, although there are some specialized tests available to evaluate the innate immune system. Testing focuses on T and B cells, measuring their numbers, appearance, and function. Cell production is measured by flow cytometry,[159] cellular appearance by examination of the cells themselves, and cellular function by challenge. Hazlehurst Tr. at 579A-81A.

Evaluation begins with a battery of tests, including a complete blood count ["CBC"], differential,[160] a chemistry panel,[161] urinalysis, and an immune panel.[162] Cedillo Tr. at 874A-75A. Cell counts include T cells, B cells, and NK cells. Testing of immunoglobulin (B cell) levels, including subtypes, is a method to determine if a child has a profound immunodeficiency. Immunoglobulin testing shows whether the child's body can make antibodies.

Children may have normal B cell counts, but poor immune function. Immune system function can be measured two ways. Th1 response (the cell-mediated arm of the immune system) is measured by the *in vitro* reaction of the cells to a stimulus. Th2 response (the humoral arm of the immune system) is measured by determining how well the B and T cells communicate. If antibodies are produced in response to a stimulation with an agent to which the child has been exposed, then that arm of the immune system is working. Testing immune response to particular pathogens, such as those found in vaccines, is a better measure of whether the child's immune system is functional, because an antibody response demonstrates that the T cells can recognize the pathogen, and that they can tell the B cells to produce antibodies to the antigens present. Hazlehurst Tr. at 579A-81A; Cedillo Tr. at 2209A-10A.

Proliferation studies are one type of *in vitro* immune system testing. In proliferation studies, extracted lymphocytes are treated with growth factors and specific

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[159] Flow cytometers measure the percentage and absolute numbers of lymphocytes present in a sample. It is important to measure both because in a child who is lymphopenic (who has a very low number of lymphocytes), the relative percentages are a less valid reading. Cedillo Tr. at 2218A-19A. Flow cytometry is used for a variety of diagnostic purposes, including testing for cancer and transplant problems, with consistent and reliable results. Cedillo Tr. at 2214A-15.

[160] A differential includes the percentage of monocytes, macrophages, T cells, and B cells present in the lymphocytes. Cedillo Tr. at 875A.

[161] A chemistry panel includes tests of liver and renal function. Cedillo Tr. at 875A.

[162] An immune panel would include B and T cells counts with subset analysis, serum immunoglobulin levels with subclasses, and testing for response to specific antigens, vaccines, and mitogens. Mitogens are substances that cause lymphocytes to proliferate. DORLAND'S at 1162. By comparing responses to common antigens (ones to which a substantial portion of the population has been exposed), it is possible to determine if the individual's immune system is responding properly. Negative responses to common antigens suggest that the immune system is abnormal. Cedillo Tr. at 875A-76A.

stimulants. Three mitogens, phytohemagglutinin, Concavalin A, and poke weed, are commonly used because they are known to activate normal T and B cells to divide. If the T and B cells are abnormal, they will not divide. Cedillo Tr. at 2219A-22A.

The immune status of an individual is not a static entity. It changes from day to day and week to week, over a lifetime. Cedillo Tr. at 1799-1800A, 2208A. For this reason, initial findings of immune abnormalities should always be followed with a repeat test. Cedillo Tr. at 2208A.

b. Relevant Norms for Test Results.

Doctor McCusker explained that the "normal" numbers of B cells, CD4 T cells, and CD8 T cells change as a child ages. In assessing a child's immune system, it is necessary to use age-appropriate norms to determine if it is functioning properly.[163] Doctor Ward agreed, testifying that what is normal for children changes rapidly from birth to 18 years of age. His testimony was illustrated in Cedillo Res. Ex. Z, Tab 4,[164] a chart which reflects that the mean number of CD4 T cells at ages 12-18 years is approximately 1/3 of the mean number at three to six months of age in healthy children in the United States. Cedillo Tr. at 1799-1801. As illustrated by Cedillo Res. Tr. Ex. 12, at 3, a chart reprinted from Cedillo Res. Ex. Z, Tab 4, cell counts for CD4, CD8, and B cells change significantly in the first 12 years of life. The number of CD4 cells declines by about one-third between birth and 12 months, and by half between birth and ages two to six. Cedillo Tr. at 1800A.

Doctor Byers testified that normal ranges from one laboratory cannot be easily compared to another laboratory's normal ranges because different labs use different reagents and different instruments. Cedillo Tr. at 885A. Doctor McCusker challenged this testimony, pointing out that pediatric immunologists in the U.S. and Canada use the same normal pediatric values, and that the normal ranges have not appreciably changed since 1992. She illustrated her testimony with the 1992 normal ranges for lymphocyte testing (Cedillo Res. Tr. Ex. 16 at 4) and the more current norms (Cedillo Res. Tr. Ex. 16 at 3). Doctor McCusker also explained that repeated assays on the same patient should use the same laboratory, but that accredited laboratories use the same reference samples, and, thus, ensure that their laboratory values are pegged to

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[163] Doctor Byers, an immunologist who does not treat children, asserted that it is acceptable to assess a child's immune status using adult parameters for normal cell numbers. Cedillo Tr. at 995. Both Dr. Ward and Dr. McCusker disagreed with this statement. Cedillo Tr. at 1799-1800A; 2211. Considering their relative qualifications, and the support found for their testimony in other exhibits (*see, e.g.*, A. Gasparoni, *et al., Age-Related Changes in Intracellular TH1/TH2 Cytokine Production, Immunoproliferative T Lymphocyte Response and Natural Killer Cell Activity in Newborns, Children and Adults*, BIOL. NEONATE 84: 297-303 (2003), filed as Cedillo Res. Ex. Z, Tab 6), I credit their testimony over that of Dr. Byers on this point.

[164] W. Shearer, *et al.*, *Lymphocyte subsets in healthy children from birth through 18 years of age: The Pediatric AIDS Clinical Trials Group P1009 study,* J. ALL. CLIN. IMMUNOL. 112: 973-80 (2003).

the reference samples. Cedillo Tr. at 2261A. Given a choice between using adult values from the same laboratory or children's values from another laboratory, using the adult values would violate the standard of care. Cedillo Tr. at 2266-67. Once again, I adopt Dr. McCusker's testimony on this topic, given her greater clinical experience.

c. Interpreting Results.

Doctor Byers testified that abnormally elevated levels of IgG2 and IgG4 are consistent with Th1/Th2 skewing and that an abnormally elevated CD4:CD8 ratio is indicative of an autoimmune process. Cedillo Tr. at 883A-84A. She also testified that an elevated CD20 count is indicative of an elevated B cell precursor population, consistent with bone marrow toxicity. Cedillo Tr. at 884A.

Doctor McCusker disagreed. She pointed out that there is no clinical significance attached to elevated IgG2 levels. Some case reports or case series suggest that specific IgG2 antibodies are elevated in patients with periodontal disease. Cedillo Tr. at 2224A. IgG2 elevations are associated with a Th2 skewing in mice, but not in humans. She was unable to find any support in medical literature that subclass changes are related to autoimmunity, and only one article that speculated that they might be.[165] Cedillo Tr. at 2258-60A.

IgA deficiency means that a person has no IgA. Most laboratories define this as less than 7-10 milligrams per deciliter. Approximately one in five hundred individuals is IgA deficient. Most of these individuals have no clinical evidence of disease, and the IgA deficiency is simply an incidental finding. When there is evidence of disease, an IgA deficiency is associated with chronic and persistent sinusitis, ear infections, and pharyngitis, but not with an increased number of colds. Snyder Tr. at 587A-88A.

C. TCVs and Immune Response.

1. The Mercury Theory.

Petitioners contend that the ethylmercury in TCVs caused, or contributed to, "immune dysregulation" in a subset of children receiving TCVs. Under their theory, this immune dysregulation, coupled with the purported immunosuppressive effects of the measles vaccine strain virus, hampered the children's ability to clear the measles virus from their systems. They allege that the measles virus persisted and caused gut disorders and autism.

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[165] V. Trajkovski, *et al., Plasma Concentrations of Immunoglobulin Classes and Subclasses in Children with Autism in the Republic of Macedonia: Retrospective Study*, CROAT. MED. J. 45: 746-49 (2004), filed as Cedillo Res. Ex. Z, Tab 11, at 748.

Based primarily on the testimony and report of Dr. Aposhian,[166] petitioners argued that: (1) ethylmercury[167] is harmful to the immune system; (2) the amounts of ethylmercury contained in TCVs can suppress the immune system; and (3) this effect is enhanced in children with a "mercury efflux disorder." Snyder Pet. Post-Hearing Brief at 20.

Doctor Byers provided some additional support for the proposition that TCVs can cause immunosuppression, and that the combined effect of TCVs and the MMR vaccine disables the immune system sufficiently to allow the measles virus to persist. Additionally, petitioners argued that her testimony established that TCVs can damage dendritic cells. Snyder Pet. Post-Hearing Brief at 21.

Petitioners' primary witness on mercury and its effects was Dr. Aposhian, a toxicologist.[168] Respondent countered Dr. Aposhian's testimony with that of Dr. Brent, a medical toxicologist. Doctor Byers' testimony about mercury's effects on the immune system was not drawn from her expert report, her publications, or her personal research. It appeared that she drew her understanding of mercury's effects from several scientific journal articles that she had read.

In contrast to the testimony of both of petitioners' witnesses, Dr. Brent offered clear and focused testimony during both direct and cross-examination. His testimony was based on his experience in diagnosing and treating mercury poisoning, and was supported by the medical literature filed. Doctor McCabe, an immunotoxicologist, was eminently qualified to opine on both mercury in general and its effects on the immune system in particular.

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[166] I note that Dr. Kennedy testified that heavy metals can have an immunosuppresive effect, but qualified that statement with the caveat that it was based on his reading, not his expertise. Cedillo Tr. 776-783. He did not testify directly about thimerosal or ethylmercury's effects. I have thus accorded his opinion on this topic little weight.

[167] Thimerosal is a molecule composed of ethylmercury and thiolsalicylate (49.6% mercury by weight). IOM 2004 Report, Cedillo Res. Ex. JJ, at 36; A. Agrawal, *et al.*, *Thimerosal induces TH2 responses via influencing cytokine secretion by human dendritic cells,* J. LEUKOCYTE BIO. 81: 474-82 (2007) ["Agrawal"], filed as Cedillo Pet. Ex. 55, Tab A.) Once administered, the weak bond between ethylmercury and thiosalicylate breaks, as thimerosal rapidly metabolizes into ethylmercury and thiosalicylate. Cedillo Tr. at 2313.

[168] In *Hazlehurst,* Dr. Cobier testified about the toxic effects of thimerosal. Hazlehurst Tr. at 285A-288A. It was apparent, both from his testimony and from his curriculum vitae, that his opinions were based on his reading of scientific literature rather than any expertise in mercury toxicology. Therefore, I gave his testimony on this subject little weight.

2. Mercury Toxicology.

a. Exposure and Species of Mercury.

Everyone is exposed to mercury on a daily basis. Mercury is present in the air we breathe, some of the food we eat, the soil we walk on, and in the water we drink, albeit in extremely small amounts. Cedillo Tr. at 2473-74. In industrialized societies, power plant emissions add to the naturally occurring mercury from volcanic emissions and other sources.[169] Seafood accounts for the majority of ingested mercury. Mercury vapor released from dental amalgams also contributes to mercury exposure in humans. Other sources of mercury exposure include pesticides and fungicides. Seed wheat treated with a fungicide, and inadvertently ingested by farmers unable to read the warning labels, accounted for numerous cases of mercury poisoning in Iraq in 1971-72,[170] while seed rice in China caused a similar disaster in 1974.[171] Mercury poisoning may also occur as a by-product of mining. *See* T. Clarkson, *The Three Modern Faces of Mercury*. ENVIRON. HEALTH. PERSPECT. 110:11-23 (2002) ["Clarkson 2002"], filed as

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[169] L. Trasande, *et al., Public Health and Economic Consequences of Methylmercury Toxicity to the Developing Brain*, ENVIRON. HEALTH PERSPECT. 113(5): 590-96 (2005), filed as Cedillo Res. Ex. L, Tab 57.

[170] F. Bakir, *et al., Methylmercury poisoning in Iraq,* SCIENCE 181:2 30-241 (1973) ["Bakir" or "Iraqi study"], filed as Cedillo Pet. Ex. 55, Tab D. This widely cited article reported the effects of oral ingestion and prenatal exposure to methylmercury as the result of eating bread made from seed grain treated with methylmercury. Central nervous system damage, characterized by loss of sensation in hands and feet, paresthesia around the mouth, ataxia, slurred speech, diminution of vision, and loss of hearing, were common symptoms, with extremity numbness and paresthesia as the first symptoms noted. Severe poisoning resulted in blindness, coma, and death. Prenatal exposure resulted in mental retardation with cerebral palsy. Those infants prenatally exposed had higher concentrations of methylmercury in their blood than did their mothers. Onset of parasthesia occurred, on average, at 40 mg of exposure, although parathesia occurred at doses as low as 25 mg of methylmercury. Threshold doses for ataxia, dysarthria, deafness, and death were 55, 90, 170, and 200 mg of Hg, respectively. Of note, the abbreviation "mg" represents milligrams, or one-thousandth of a gram, as compared to "µg" which represents a microgram, or one millionth of a gram. *See* Neil M. Davis, MEDICAL ABBREVIATIONS ["MED. ABBREV."], 12TH Ed. (2005), at 394.

[171] J. Zhang, *et al., Clinical Observations in Ethyl Mercury Chloride Poisoning*, AM. J. INDUSTRIAL MED. 5: 251-58 (1984) ["Zhang"], filed as Cedillo Res. Ex. L, Tab 60. This was a retrospective analysis of oral ethylmercury poisoning by contaminated seed rice. Onset of symptoms began between 7-15 days after ingestion. The symptoms observed in over 10% of the patients were (in order of most frequent symptom): weakness, loss of appetite, dizziness, nausea, abdominal pain and diarrhea, fever, numbness of extremities, paresthesia, ataxia, vomiting, thirst, unsteady gait, headache, insomnia, fatigue and sleepiness, heart palpitation, inability to walk, polyuria, and chest pain. Those hospitalized had weakness, loss of appetite, nausea and vomiting, dizziness, speech disturbance, incapability of standing, abdominal pain and diarrhea, and tinnitus. The signs displayed by more than 20% of those hospitalized included muscular weakness, fever, unsteady gait, decreased tendon reflexes, emaciation, hepatomegaly, listlessness, impaired speech, paralysis in lower extremities, increased tendon reflexes, and coma. Mild cases were estimated to have ingested 0.5-1.0 mg/kg body weight; moderate at 1.0-2.0 mg/kg body weight; severe cases at 2.0-3.0 mg/kg body weight and the one lethal case at 4.0 mg/kg body weight. Doctor Brent testified that these patients had ingested between 35,000 and 280,000 µg of ethylmercury.

Cedillo Pet. Ex. 55, Tab G, at 12.

Mercury readily forms compounds with other substances. The various mercury compounds and elemental mercury are often referred to as "species" of mercury. Elemental mercury and its non-carbon-containing compounds are classified as inorganic mercury. Mercury compounds containing carbon are classed as organic forms of mercury. Elemental mercury is found in air and dental amalgams. Inorganic mercury can be found in air, water, and food, in the form of mercury vapor or mercury salts. Organic mercury includes methylmercury (found primarily in fish) and ethylmercury. Cedillo Tr. at 2343-44. Ethylmercury from TCVs is the primary source of ethylmercury exposure. Breast milk contains mercury from the mother's dental amalgams, ingested mercury from water and food, and from the mother's exposure to TCVs and other mercury-containing medical products.[172] Once in the body, both elemental and organic mercury compounds are metabolized. Some of the mercury is excreted, primarily in feces and urine, and some is converted to mercuric mercury (inorganic mercury), which binds to body tissues and is thus less readily excreted than organic mercury.

Thimerosal, the form of mercury found in vaccines, has been used extensively in pharmaceutical products since the 1920s.[173] Although it was removed from most vaccines by 2001, it continues to be used as an antimicrobial in multidose vials of some vaccines. IOM 2004 Report, Cedillo Res. Ex. JJ, at 36-37. A study performed in 1931 established its safety, based on the standards of the time. Cedillo Tr. at 2312-13. Doctor Aposhian testified that, in 1982, the Food and Drug Administration ["FDA"] found that thimerosal was ineffective and, in 2007, that there was inadequate data to establish its safety and effectiveness. Cedillo Tr. at 88A-89. Doctor Brent testified that Dr. Aposhian had misinterpreted the FDA action, which was not relevant to the use of thimerosal in vaccines. Cedillo Tr. at 2314A-16. Reviewing the two exhibits Dr. Aposhian discussed,[174] I conclude that Dr. Brent was correct.

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[172] According to one study, children who are breast fed received twice as much methylmercury from breast milk than from ethylmercury in vaccines. Cedillo Tr. at 2476. *See* R. Marques, *et al.,Hair mercury in breast-fed infants exposed to thimerosal-preserved vaccines*, EUR. J. PEDIATR. DOI 10.1007/s00431-006-0362-2 (2007), filed as Cedillo Res. Ex. L, Tab 39.

[173] Thimerosal was used in WWII as a preservative for blood plasma, and was used for many years in over-the-counter disinfectants such as merthiolate. Cedillo Tr. at 2312-13.

[174] Cedillo Res. Tr. Ex. 18, 47 F.R. 436 (1982) (notice of proposed rulemaking regarding banning the use of mercury-containing over-the-counter drug products) and Cedillo Res. Tr. Ex. 19, 21 C.F.R. § 310.545 (April 11, 2007). The 1982 FDA action was an assessment of the safety and efficacy of thimerosal-containing disinfectants such as merthiolate for use on wounds. The assessment was performed because of concerns that overdosing could occur, that thimerosal was not effective in wounds containing pus, and that there was a potential for allergic reactions. The 2007 FDA action involved a listing of some 700 drug products sold over the counter for which there was inadequate data to establish their safety and effectiveness. The list, organized by the use to which the product was commonly put, included camphor, aspirin, Vitamin E, zinc oxide, menthol, peppermint oil, garlic, and thimerosal. Thimerosal's inclusion on the list had nothing to do with its use as a preservative in vaccines.

b. Toxicokinetics.

Generally speaking, the different species of mercury have different toxicological properties. Mercury is the metal with the most diverse effects among its different species. Cedillo Tr. at 2342A-43, 2487-88. Unfortunately, much of the evidence submitted by petitioners on the harmful effects of mercury involved studies and reports dealing with exposure to methylmercury, not the ethylmercury found in thimerosal. In order to show that such studies and reports are relevant to the issues before this court, petitioners must first show that the two substances have similar toxicological properties and similar effects on human metabolism. Their efforts to do so were not entirely successful. Although there are similarities between the two species of mercury and their effects, the differences are significant. In assessing ethylmercury's effects on the immune and central nervous systems, I relied upon the amply supported testimony that it is not scientifically valid to use the toxicological properties of methylmercury to determine the effects of similar doses of ethylmercury. Cedillo Tr. at 2346.

Doctor Brent used the analogy of the effects of methyl alcohol (wood alcohol) and ethyl alcohol (the type of alcohol found in beer, wine, and other alcoholic beverages) to illustrate problems in extrapolating effects across species. Both alcohol species will produce intoxication, but methyl alcohol causes delirium, blindness, and death, even in very small amounts. Cedillo Tr. at 2345-46. Doctor Brent's example illustrates two fundamental principles of toxicology: toxicokinetics and dose response. Differences between the toxicokinetics of ethyl and methylmercury, and the dose response of each species of mercury in humans, make extrapolations of data from methylmercury exposure to ethylmercury exposure unreliable because chemically similar substances do not always behave similarly *in vivo*.

Although some aspects of mercury metabolism are similar among the species of mercury, significant differences exist. One or two drops of dimethylmercury on a laboratory worker's glove was so toxic that it caused her death from mercury poisoning months later.[175] Cedillo Tr. at 71-72A. In contrast, some of the Iraqis and Chinese who ingested contaminated seed grain had significant levels of mercury in their bodies, without apparent effect. Cedillo Tr. at 2487-91.

Both mercury vapor and methylmercury have been intensively studied. However, far fewer studies exist on the effects of ethylmercury. Cedillo Tr. at 2343. One of the few studies examining ethylmercury's effects was the Burbacher study, filed as Cedillo Res. Ex. L, Tab 12.[176] This study compared mercury levels in infant monkeys

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[175] D. Nierenberg, *et al., Delayed Cerebellar Disease and Death after Accidental Exposure to Dimethylmercury*, NEJM 338: 1672-76 (1998), filed as Cedillo Pet. Ex. 55, Tab LL.

[176] T. Burbacher, *et al., Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methyl Mercury or Vaccines Containing Thimerosal.* ENVIRON HEALTH PERSPECT 113: 1015-21 (2005) ["Burbacher"].

given either oral methylmercury (because most methylmercury exposure comes through food) or intramuscular injections of thimerosal. In three weeks, the monkeys were given roughly the amount of thimerosal that a human infant would receive in six months of vaccinations,[177] on a per kilogram basis. The researchers then assessed the toxicokinetics of the exposures. The half-life[178] for ethylmercury in primates was about eight days, comparable to seven days in humans.[179] Cedillo Tr. at 2330, 2470-71. The half-life of methylmercury in primates was 25 days, more than three times longer.[180]

The Burbacher study also examined the amount of each species of mercury that entered the brain, finding that about three times more methylmercury did so. Of the amounts of each species that entered the brain, ethylmercury was eliminated nearly twice as fast as methylmercury. However, a higher percentage of the ethylmercury that entered the brain was converted there to inorganic mercury than that of methylmercury. Once converted to inorganic mercury from either source, it was eliminated very slowly. Cedillo Tr. at 2471-74; Cedillo Res. Ex. L at 13. The authors of the Burbacher study concluded that methylmercury is "not a suitable reference for risk assessment from exposure to thimerosal."

Other studies have demonstrated that ethyl and methylmercury have affinities for different body organs, with ethylmercury targeting both the kidneys and the brain and methylmercury specifically targeting the brain. Different amounts of each species are required to produce mercury intoxication. The Burbacher study demonstrated that more ethyl than methylmercury is required to produce the same effect. The 1985 Magos study, filed as Cedillo Pet. Ex. 55, Tab FF,[181] had similar results. More ethylmercury than methylmercury was required to produce a given amount of damage to the brain in rats. Cedillo Tr. at 2489-90. Only rats exposed to methylmercury had widespread granular layer damage in the cerebellum, indicating that organic mercury

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[177] The compressed period of administration, as compared to the vaccination schedule for human infants, did not permit the same amount of excretion of mercury between doses. Thus, the results are not directly comparable to the levels of mercury that could be expected in human infants, even assuming that human infants metabolize mercury in the same manner as primate infants. *Id*. at 1015.

[178] "Half-life" (sometimes called "half-time") refers to the period of time for half of a given amount of a substance to be eliminated from the body. DORLAND'S at 810.

[179] A research team examining the clearance rate of ethylmercury in human infants receiving TCVs found a seven day half-life for ethylmercury. *See* M. Pichichero, et al., Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study, LANCET 360: 1737-41 (2002) ["Pichichero"], filed as Cedillo Pet. Ex. 55, Tab NN.

[180] Burbacher, Cedillo Res. Ex. L, Tab 12. The half-life of methylmercury in humans appears to be significantly longer than its half-life in primates. The mean half-life in the Iraqi seed wheat disaster was 65 days, with ranges from 40-105 days. Bakir, Cedillo Pet. Ex. 55, Tab D. Doctor Brent's report indicated the half-life for methylmercury via dietary exposure was 50-70 days. Cedillo Res. Ex. L, at 13, n.7.

[181] L. Magos*, et al., The comparative toxicology of ethyl- and methylmercury*, ARCH. TOXICOL. 57: 260-67 (1985) ["Magos 1985"].

was not responsible for the brain damage. Cedillo Pet. Ex. 55, Tab FF (abstract). *See also* Clarkson 2002, Cedillo Pet. Ex. 55, Tab G, at 13 (methylmercury produces more severe brain damage).

The clinical effects of methyl and ethylmercury also differ. With methylmercury, almost all of the clinically observable effects are in the central nervous system. With ethylmercury, the rapid separation of the mercury from the ethyl group results in a faster conversion to inorganic mercury, which primarily affects the kidneys. It also affects the central nervous system. The central nervous system symptoms commonly associated with both species of mercury include tunnel vision, tremor, and paresthesia. Cedillo Tr. at 2487-89.

As Clarkson and Magos, two of the premier researchers into mercury toxicology, summarized: "[E]thylmercury appears to be roughly similar to methylmercury in terms of its initial distribution to the blood compartment and in its fecal excretion. Methyl- and ethylmercury differ sharply in the patterns of tissue deposition and in the rate of metabolism to organic mercury. These large differences in disposition and metabolism indicate that the data on methylmercury are not a suitable reference for risk assessments for thimerosal." [182] Clarkson and Magos 2006, Cedillo Pet. Ex. 55, Tab H, at 647.

c. Dose Response, Efflux Disorders, and Hypersusceptibility.

(1) Dose Response.

Doctor Brent called the principle of dose response "the most fundamental principle of toxicology." Cedillo Tr. at 2337. Dose response is the concept that virtually any substance can be harmful or even lethal in sufficiently high doses. Excessive water consumption can lead to death, even though water consumption is absolutely essential to human life.[183] Cyanide is well known as a poison, but everyone is exposed to some cyanide without ill effects in the air we breathe. Cedillo Tr. at 2335-37. CLINICAL ENVIRONMENTAL HEALTH AND TOXIC EXPOSURES, a well respected textbook on occupational toxicology,[184] states: "No matter what the compound's potency or how little compound is necessary to produce an effect, its respective toxic dose threshold must be surpassed to produce toxicity." Cedillo Res. Tr. Ex. 20, at 4.

Doctor Aposhian disagreed about the importance of the concept of dose

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[182] T. Clarkson and L. Magos, *The Toxicology of Mercury and Its Chemical Compounds*. CRITICAL REV. TOXICOL. 36: 609-62 (2006), filed as Cedillo Pet. Ex. 55, Tab H ["Clarkson and Magos 2006"].

[183] Doctor Aposhian used the same example of excess water consumption. Cedillo Tr. at 130. This is curious, in view of Dr. Aposhian's testimony that dose response is an outmoded concept.

[184] J. Sullivan and G. Krieger, CLINICAL ENVIRONMENTAL HEALTH AND TOXIC EXPOSURES, (2d ed.) ["Sullivan and Krieger"], filed as Cedillo Res. Tr. Ex. 20.

response, testifying that it was an outmoded concept. He noted that factors other than the dose may affect individual response. Cedillo Tr. at 129B-131A.

On this point, both experts appear to be correct, but incompletely so. Doctor Brent is correct that dose is the most important factor in determining if a given substance can or did cause harm, but individual characteristics may also play a role. Dose response to a substance can be affected by many factors, including: co-administration of other substances, weight, metabolism, gender, and genetic makeup. One person stung by a bee may go into anaphylactic shock; another may merely experience some temporary pain or discomfort. As Sullivan and Krieger noted: "From a practical perspective, there are two types of dose-response relationships: (1) that which describes the response of an *individual* to varying doses of a chemical, often referred to as "graded" responses because the measured effect is continuous over a range of doses, and (2) that which characterizes the distribution of responses to different doses in a *population* of individuals." (emphasis original). Cedillo Res. Tr. Ex. 20 at 18.

The dose of mercury required to cause clinically apparent symptoms differs among different species of mercury. The amount of mercury at which clinical symptoms appear is referred to as mercury intoxication. Intoxication means that an individual has enough of a substance in his system to cause an adverse or toxic effect. Cedillo Tr. at 2484A-85. The point at which an adverse effect occurs varies from person to person; all the points at which individuals experience adverse effects form a bell curve. Cedillo Tr. at 2485-87.

(2) Reference Dose ["RfD"].

Both Dr. Aposhian and Dr. Brent agreed on the concept and definition of the term "reference dose." The term is used by the Environmental Protection Agency ["EPA"] to mean the daily dose of a substance, as averaged over a lifetime, that would not be expected to have an adverse effect. The most important concept regarding reference dose is that it represents an average over a lifetime. On some days, the reference dose might be exceeded, while, on others, the reference dose would not be reached. Cedillo Tr. at 66-66B, 85A, 2346-47. The reference dose does not reflect the point at which toxicity will occur. Cedillo Tr. at 2348-50.

The EPA RfD is 0.1 μg[185] of methylmercury per kilogram per day. Cedillo Tr. at 84A. The reference dose is substance specific; there is no established reference dose for either ethylmercury or thimerosal. Cedillo Tr. at 2347.

The reference dose for methylmercury was established based on data obtained

[185] The symbol "μg" was routinely used in exhibits as an abbreviation for "microgram" (sometimes abbreviated as "mcg"), meaning one millionth of a gram. It should not be confused with the abbreviation "mg" or milligram, which represents one-thousandth of a gram. *See* MED. ABBREV. at 394.

from victims of the mercury-contaminated seed wheat disaster in Iraq.[186] The data were later refined by the Faroe Islands study.[187] The reference dose is derived by finding the lowest point at which adverse effects of a substance are observed and reducing that dose by a factor of 10. Cedillo Tr. at 2348-50.

There is no scientific basis for applying the reference dose from methylmercury to doses of thimerosal. Cedillo Tr. at 2347. Even if there were, Dr. Aposhian misapplied the reference dose concept during his testimony in *Cedillo*. He testified that when Michelle Cedillo was one day old, she weighed approximately 3.6 kilograms and received a dose of 12.5 µg of mercury from her first hepatitis B vaccination, which amounted to 3.5 µg of mercury per kilogram. Cedillo Tr. at 85A. This was correct. On that date, the amount of ethylmercury she received exceeded the reference dose for methylmercury. However, Dr. Aposhian misapplied the reference dose concept when he stated that Michelle received it "per day" and that she therefore received 35 times the EPA RfD.[188] In fact, she received a bolus dose on that day (and on the dates of several other vaccinations), not "per day." There is no RfD established for ethylmercury; the EPA RfD is for methylmercury. Assuming Michelle gained no weight and ingested no mercury from other sources, her cumulative exposure in one month would be roughly that of the RfD for methylmercury. Cedillo Tr. at 2347-48.

(3) Hypersusceptibility[189] and Efflux Disorders.[190]

A number of epidemiological studies have failed to find any evidence that thimerosal exposure plays any role in the development of autism. Further, there is no

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[186] G. Rice, *et al.*, *Derivation of U.S. EPA's Oral References Dose (RfD) for Methylmercury*, DRUG CHEM. TOXICOL. 23(1): 41-54 (2000), filed as Cedillo Res. Ex. L, Tab 48.

[187] *See* P. Grandjean, *et al., Cognitive Deficit in 7 Year-Old Children with Prenatal Exposure to Methylmercury*, NEUROTOXICOL. TERATOL. 19: 417-28 (1997), filed as Cedillo Pet. Ex. 55, Tab S, and P. Grandjean, *et al., Cognitive Performance of Children Prenatally Exposed to "Safe" Levels of Methylmercury*, ENVIRON. RES., Sect A 77: 165-72 (1998), filed as Cedillo Pet. Ex. 55, Tab T. In terms of the adverse effects observed, the Faroe Islands study found very subtle, subclinical deficits in memory and language in children who were otherwise normal. Cedillo Tr. at 2348-50.

[188] This was not simply a misstatement by Dr. Aposhian. He resisted efforts during cross-examination to have him quantify the level of ethylmercury from TCVs in Michelle at any one time, and ignored the elimination process for mercury. Cedillo Tr. at 195-97.

[189] "Hypersusceptible" was not defined by Dr. Aposhian. According to Dr. Brent, hypersusceptible individuals manifest toxic responses to a dose of an agent that does not produce any response in the general population. Cedillo Tr. at 2481.

[190] "Efflux" refers to molecules leaving the body. In this context, it refers to an inability to excrete mercury. Cedillo Tr. at 2480.

evidence that mercury exposure is related to autistic symptoms.[191] Therefore, petitioners must postulate a small group of children with ASD who are unusually sensitive to the effects of mercury or unable to excrete it properly, because epidemiologic studies are unable to rule out the effect of TCVs on a small, "hypersusceptible" group of children. Petitioners also contend that many children with autism have a mercury efflux disorder, rendering them more sensitive to its effects. The scant evidence that autistic children have an inability to excrete mercury is contradicted and outweighed by other evidence that they do not differ from their typically developing peers with regard to mercury excretion.

Efflux disorders do exist. Wilson's disease, a genetic disorder, involves the inability to excrete copper. Cedillo Tr. at 95A; 2363-64. However, mercury efflux disorder is not an ICD diagnosis and is not currently recognized as a disorder by the medical community at large. Cedillo Tr. at 2361-62A. The ASD population has been extensively screened for genetic susceptibilities, but nothing in that screening indicates a susceptibility to mercury or other chemicals. Cedillo Tr. at 2364. Doctor Brent testified that a mercury efflux disorder is, at best, a hypothetical disorder. Cedillo Tr. at 2351.

Genetic "susceptibilities" aside, it is true that not everyone responds to a chemical compound in precisely the same way. As an example, Dr. Brent used the example of the amount of alcohol required to render someone unconscious. Plotting the dose required for a population results in a bell curve. If there is truly a susceptible population, the curve shape changes to two bell shaped curves. *See* Cedillo Res. Tr. Ex. 17, at 44 (a theoretical example of the double bell curve demonstrating hypersusceptibility;) Cedillo Tr. at 2364-65, 2481-82.

Aside from Dr. Aposhian's opinion that at least some autistic children suffer from a mercury efflux disorder (Cedillo Tr. at 70), the primary evidence for the existence of such a disorder in the general population stems from articles about acrodynia. The evidence that autistic children, as a group, have difficulty excreting mercury comes from three studies: one by Dr. Holmes (involving hair samples), one by Dr. Adams (involving baby teeth), and one by Dr. Bradstreet (involving urinary excretion after chelation[192]).

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[191] *See* S. Parker, *et al., Thimerosal-Containing Vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data*, PEDIATRICS 114(3): 793-804 (2004), filed as Cedillo Pet. Ex. P, Tab 117. This literature survey examined twelve studies of the relationship of thimerosal to autism, and concluded that there is no reliable evidence of a link between TCVs and autism, and that the pharmacodynamics of ethylmercury make such an association unlikely. *See also* Cedillo Tr. at 2369-70.

[192] Chelation is the use of chemicals to break the bond formed between some heavy metals and body tissue. Those being chelated are treated with reactive chemicals that break the bond with tissue and cause the heavy metals to bind instead to the chelating agent. *See generally,* H. Aposhian and M. Aposhian, *Meso-2, 3-dimercaptosuccinic acid: Chemical, Pharmacological and Toxicological Properties of an Orally Effective Metal Chelating Agent,* ANN. REV. PHARMACOL. TOXICOL. 30: 279-306 (1990), filed as Cedillo Pet. Ex. 55, Tab B; Snyder Tr. at 769A. Chelation therapy has been approved to reduce lead levels in children and in cases of mercury poisoning. Its use in treating children with ASD remains highly

(a) Evidence for a Mercury Efflux Disorder.

Doctor Aposhian contended that acrodynia was evidence of a hypersusceptibility to mercury in a subset of the population. Acrodynia is a condition characterized by a bright pink color of the hands and feet (giving it the name "Pink disease"). Its symptoms are similar to conditions also caused by acute high dose exposure to inorganic mercury. They do not resemble symptoms of autism.[193] The cause of acrodynia was eventually identified as teething powder containing calomel, which is mercurous mercury, a form of inorganic mercury. Cedillo Tr. at 2366A-68.

In discussing acrodynia, Dr. Aposhian repeated a figure that frequently appeared in the medical literature, that only 1 in 500 children exposed to the teething powders developed the condition. Doctor Aposhian considered this figure to be evidence that some children were hypersensitive to mercury. An examination of the article most often cited for this figure, found at Cedillo Court Ex. I,[194] reveals that the figure was not derived from any scientifically controlled study. Indeed, because the amount of teething powder administered by parents could not be measured retrospectively, those afflicted were as likely to have been those who received the highest doses of mercurous mercury, rather than representing children with a mercury efflux disorder.[195] A study[196] that measured urinary mercury levels in children suffering from acrodynia identified very high levels, between 200 to 2,500 µg/L of urine, in the majority of those children.[197]

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controversial. Cedillo Tr. at 1452A. Although parents often identify chelation, according to Dr. Aposhian, as the autism therapy with the most positive behavioral results (*see* Cedillo Pet. Ex. 61, at 25), there are no scientifically controlled studies testing its efficacy in treating autism. Cedillo Tr. at 2355-61. Doctor Aposhian did not identify any source for this assertion.

[193] Although Dr. Aposhian's report cited to an article by S. Bernard, *et al.*, (*Autism: A novel form of mercury poisoning,* MED. HYPOTHESES 56(4) 462-71 (2001), filed as Cedillo Res. Ex. L, Tab 10) that contended the symptoms of acrodynia and mercury poisoning were similar, a comparison of the primary symptoms of autism and those of acrodynia clearly indicates that the two conditions are not similar. Doctor Brent's report (Cedillo Res. Ex. L at 4-5) called this article's premise "wholly insupportable." *See also* Nelson and Bauman, Cedillo Pet. Ex. L, Tab 43.

[194] J. Warkeny and D. Hubbard, *Acrodynia and Mercury*, J. PEDIATRICS 42(3): 365-86 (1953) ["Warkeny"], filed as Cedillo Court Ex. I. This article was often cited as the source of the 1-in-500 figure; the court obtained the article to determine how that figure was derived.

[195] Doctor Brent testified that the 1-in-500 number had been carried forward and requoted in the literature dealing with acrodynia. The most likely explanation is not a hypersusceptible population, but rather the dose of teething powder that the children received. There were no dose-response studies with regard to acrodynia. Cedillo Tr. at 2483A.

[196] Cited in Warkeny, Cedillo Court Ex. I, at 371.

[197] Although Dr. Aposhian testified that he did not know what blood or urinary levels of mercury would be considered "normal," he said that a blood mercury level under 5 µg/L would not be of clinical concern. Cedillo Tr. at 131A. The mean normal blood mercury level in children age 1-5 in 1999-2000 was 0.34 µg/L. S. Schober, *et al., Blood Mercury Levels in US Children and Women of Childbearing Age,*

Cedillo Tr. at 2367-69.

Doctor Aposhian testified that recent research had established that a subset of the population with a genetic hypersusceptibility to mercury does exist. In support, Dr. Aposhian referred to research by Dr. James Woods at the University of Washington regarding the use of urinary porphyrins (a compound produced in biosynthesis and excreted in urine) as a biomarker for mercury body burden. Cedillo Tr. at 92A-94A; Snyder Res. Ex. T at 2 (Report of Dr. McCabe). The articles concerning Dr. Woods' research, to which Dr. Aposhian referred, were not filed as exhibits in *Cedillo*, but were filed as literature attached to Dr. McCabe's report in *Snyder*.[198] Doctor McCabe's report noted that Dr. Woods' work with urinary porphyrins had not been adopted by the vast majority of metal toxicologists. Snyder Res. Ex. T at 2.

According to Dr. Cook, this research does not support Dr. Aposhian's testimony about a genetic hypersusceptibility to mercury. Cedillo Tr. at 1502A-03. He called Dr. Aposhian's testimony pure speculation. Cedillo Tr. at 1505. The Heyer paper does indicate that about 15% of dentists and dental assistants have a genetic polymorphism that affects some urinary porphyrins. It does not indicate that the polymorphism has been associated in any way with a "hypersusceptibility" to mercury, a higher body burden of mercury, any difficulty in excreting mercury, or any ill effects from mercury. The study measured the effect of the polymorphism on porphyrin excretion patterns, but came to no conclusion on whether the polymorphism had any effect on mercury toxicity. Heyer, Snyder Res. Ex. T, Tab 5, at 159, 164-65. I adopt the testimony of Drs. Cook and McCabe that there is no persuasive evidence of a mercury hypersusceptibility disorder in the general population.

(b) Evidence for Mercury Excretion Disorders in ASD.

Doctor Brent testified that there is no study in the peer reviewed[199] English

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1999-2000, JAMA 289: 1667-74 (2003), filed as Cedillo Pet. Ex. 55, Tab OO.

[198] *See* J. Woods*, et al., Urinary Porphyrin Profiles as Biomarkers of Trace Metal Exposure and Toxicity: Studies on Urinary Porphyrin Excretion Patterns in Rats during Prolonged Exposure to Methyl Mercury,* TOXICOL. APPL. PHARMACOL. 110: 464-76 (1991), filed as Snyder Res. Ex. T, Tab 3, and J. Woods*, et al., Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity,* CAN. J. PHYSIOL. 74: 210-15 (1996), filed as Snyder Res. Ex. T, Tab 4. It appears from Dr. Aposhian's testimony that he was actually referring to the Heyer study, co-authored by Dr. Woods. *See* N. Heyer, *et al., A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production,* TOXICOL. LETTS. 161: 159-66 (2006) ["Heyer"], filed as Snyder Res. Ex. T, Tab 5.

[199] Peer review involves the review of submitted manuscripts by known experts in the field. Peer reviewers are supposed to read the articles carefully to ensure that the manner in which the research was carried out and the interpretation of the results of the research are the product of due care. Papers that are published after this process have had careful review by several reviewers. Peer review clarifies and improves papers, catching errors and mislabeling. Some journals are more reliable in this process than

language scientific literature that reports a difference in blood or urinary mercury levels in autistic children as compared to controls. These are the easiest levels to measure. Cedillo Tr. at 2469. Two of the three studies that petitioners relied upon to demonstrate aberrant mercury excretion patterns in children with ASD involved hair and teeth. The third, Dr. Bradstreet's 2003 study, did involve urine, but the paper was not published in a peer reviewed and indexed journal.[200] Cedillo Tr. at 2360. All three of these studies have significant flaws that adversely affect the scientific reliability of their conclusions.

In the Bradstreet study, filed as Cedillo Pet. Ex. 55, Tab E,[201] 55 autistic children were matched for age, sex, and vaccination status with eight, non-randomly selected controls. Mean urinary mercury excretion after three days of chelation was 6.42 µg/g of creatinine[202] for the ASD children and only 1.08 µg/g of creatinine for the control children. No pre-chelation levels were determined for either group.[203] The authors conceded that they could not determine whether the higher mercury excretion levels in the ASD children were the result of higher mercury intake or a reduced ability to excrete it without chelation. Cedillo Pet. Ex. 55, Tab E, at 79.

Other problems with the Bradstreet 2003 article, as noted by Dr. Brent, involve

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others and have better reputations because of their high standards. Peer review also catches conflicts of interest to ensure that articles are not published for financial gain. Hazlehurst Tr. at 544A-46B.

[200] An indexed journal is one that is searchable by medical-scientific literature search engines. A journal may be non-indexed because it is new or because it is considered to be "insufficiently rigorous" for scientists to rely upon its publications. Cedillo Res. Ex. BB at 6. Doctor Ward noted that the Bradstreet 2003 study was published in the Journal of American Physicians and Surgeons, which, although published for over 50 years, remains non-indexed. *Id*. Medical literature may not be required as a condition precedent to finding vaccine causation. *Althen,* 418 F.3d at 1281. However, 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).

[201] J. Bradstreet, *et al.*, *A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders*, J. AM. PHYSICIANS SURGEONS 8: 76-79 (2003) ["Bradstreet 2003"]. Doctor Brent testified that this journal is not an indexed journal. Cedillo Tr. at 2360.

[202] Creatinine excretion rates are used to measure kidney function. DORLAND'S at 432-33.

[203] The failure to ascertain pre-chelation levels of urinary mercury is contrary to standard practice, as petitioners' own expert conceded. Cedillo Tr. at 166. *See also* Snyder Tr. at 769A (Dr. McCabe testified that the appropriate way to conduct chelation is to establish a baseline level before administering a chelating agent).

the huge and overlapping range of values for urinary mercury levels, the failure to control for diet between the two groups, and the statistical methodology employed. A chart on page 79 of the study reflected the urinary mercury ranges from zero to 60 µg/g of creatinine in the ASD children and from zero to 6 µg in the control group. The standard deviations exceeded the actual values reported, rendering the data essentially meaningless. Cedillo Tr. at 2357. Doctor Brent also noted that, given the large standard deviations, it was unlikely that the differences between the two groups were statistically significant. Based on the methodology described in the paper, Dr. Brent was unable to find a statistically significant result.[204] Cedillo Tr. at 2358; Cedillo Res. Ex. L, at 19.

Additionally, the control group of children was selected based on parental concerns about environmental mercury. Bradstreet 2003, Cedilo Pet. Ex. 55, Tab E, at 76. Doctor Brent testified that parents concerned about mercury are likely to restrict seafood in their children's diets, which would contribute to lower urinary mercury levels in the control children. However, the investigators failed to control for diet in the study. Cedillo Tr. at 2357-58.

The urinary excretion rates for the children with ASD reflected urinary mercury rates consistent with the general population. Cedillo Tr. at 2359. Although no study was filed to indicate what post-chelation mercury excretion rates are typical, Dr. Brent based his testimony on his experience with normal mercury levels. Cedillo Tr. at 2341, 2355.

Another problem with the Bradstreet 2003 study was that the authors failed to state whether individuals who had undergone prior chelation were excluded. Given that the study subjects were individuals treated by Dr. Bradstreet, who used multiple rounds of chelation with Colten (*see* Snyder Pet. Ex. 12, pp. 46-47,112-117, 151-52, 161-67, 543), the possibility that some of the children studied had previous rounds of chelation therapy cannot be excluded. Cedillo Tr. at 2356, 2359-2360.

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[204] I note that two of the co-authors of this study were Dr. Mark Geier and Mr. David Geier. This is not the first occasion in which other researchers have been unable to verify the validity of the Geiers' statistical analysis. *See* IOM, IMMUNIZATION SAFETY REVIEW: VACCINES AND AUTISM (Washington, DC: National Academies Press (2004)) at 55-62, 65 (calling their work unintelligible). A number of judges have had similar concerns about Dr. Geier's work. *See, e.g.*, *Graham v. Wyeth Laboratories*, 906 F.2d 1399, 1418 (10th Cir. 1990) (Dr. Geier's calculation error was of sufficient magnitude so as to warrant a new trial); *Doe v. Ortho-Clinical Diagnostics,* 440 F. Supp. 2d 465, 474 (M.D.N.C. 2006) (excluding Dr. Geier's testimony as based on "hypothesis and speculation."); *Redroot v. B.F. Ascher & Company,* 2007 U.S. Dist. LEXIS 40002 (N.D. Cal. June 1, 2007) (excluding Dr. Geier as an expert, finding his testimony "not reliable.") *Pease v. American Cyanamid Co.*, 795 F. Supp. 755, 760-61 (D. Md. 1992) (in granting summary judgment, trial judge noted inconsistencies in Dr. Geier's opinion); *Jones v. Lederle Laboratories, American Cyanamid Co.*, 785 F. Supp. 1123, 1126 (E.D. N.Y. 1992) ("the court was unimpressed with the qualifications, veracity, and bona fides" of Dr. Geier); and *Militrano v. Lederle Laboratories, American Cyanamid Co.*, 3 Misc. 3d, 523, 537-38 (N.Y. Sup.Ct. 2003) (characterizing Dr. Geier's affidavit as "conclusory and scattershot" and "undermined by many of the materials submitted in support of it").

Another group of researchers attempted to duplicate Dr. Bradstreet's study. The Soden study, filed as Cedillo Res. Ex. OO,[205] failed to find evidence that the autistic subjects had excess levels of mercury or other heavy metals. This study did not suffer from the defects noted by Dr. Brent in the Bradstreet 2003 study (Cedillo Tr. at 2357-60), although the numbers of test subjects with autism diagnoses and controls were smaller than in the Bradstreet 2003 study. To correct for one of the flaws noted in the Bradstreet 2003 study, dietary restrictions were imposed, pre-chelation (baseline) urine levels were measured, diagnoses of autism were confirmed, and those with previous chelation were excluded. Only one of the autistic children had a post-chelation urinary mercury level above the limits of detection.[206] None of the typically developing control children showed post-chelation urinary mercury levels above the limits of detection (which was 1 µg). Because of the small number of control subjects, no statistically significant comparison could be made. The authors considered it highly significant, however, that only one of the ASD subjects demonstrated a detectable level of mercury after chelation.

The Holmes study, found at Cedillo Pet. Ex. 55, Tab X,[207] compared the level of mercury in hair from the first haircut of 92 children diagnosed with autism with that of 45 age and gender matched controls.[208] The study found much lower levels of mercury in the hair of autistic children than in the hair of control children (mean of 0.47 µg in autistic subjects vs. mean of 3.63 µg in controls). Further, the mercury levels among the autistic subjects were inversely correlated with the severity of their autism, with the children with the most severe autistic symptoms having the lowest levels of mercury. If correct, these findings do lend support to the theory that children with autism have difficulty excreting mercury.

However, a major problem with the Holmes study is that the findings are in conflict with hair analysis data obtained in a very large study of mercury levels in U.S.

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[205] S. Soden, *et al., 24-Hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study,* CLIN. TOXICOL. 45: 476-81 (2007) ["Soden"].

[206] After a month of a fish-free diet, he was chelated again, and the post-chelation urinary mercury declined from 23 µg after the first test, to 5 µg after the second challenge.

[207] A. Holmes, *et al., Reduced Levels of Mercury in First Baby Haircuts of Autistic Children*, INT'L J. TOXICOL. 22: 277-85 (2003) ["Holmes"]. Doctor Aposhian testifed that another study, one he referred to as the "MIT" study, had confirmed Holmes' findings. Cedillo Tr. at 98. He was apparently referring to a post chelation measurement of hair mercury levels in three individuals, with one control. This study, which involved a new technology for measuring mercury levels, suffered from the same defects as the Holmes' study. L. Hu, *et. al.*, *Neutron Activation Analysis of Hair Samples for the Identification of Autism*, TRANSACTIONS AM. NUCLEAR SOC. 89: 681-82 (2003), filed as Cedillo Pet. Ex. 55, Tab Y.

[208] Hair analysis studies for heavy metals, and for mercury in particular, have been conducted frequently. Hair furthest from the scalp represents the oldest hair. Using hair obtained from the first baby haircut would capture the earliest mercury exposures. *See, e.g.*, Cedillo Pet. Ex. 55, Tab D (Bakir); Cedillo Pet. Ex. 55, Tab G (Clarkson 2002); and Cedillo Pet. Ex. 55, Tab T (Grandjean 1998).

children. Filed as Cedillo Res. Ex. L, Tab 41,[209] the McDowell study established that the mean hair mercury level of U.S. children ages 1-5 was 0.22 µg, which was lower than the mean levels for Holmes' autistic subjects, and much lower than the control subjects. Cedillo Tr. at 2352.

Although the McDowell study did not use first baby haircuts, comparisons between the two studies may still be made for two reasons . First, Holmes found similarly low levels of mercury in current hair levels of autistic children, prior to her study of baby hair. Cedillo Tr. at 2463-65; Holmes, Cedillo Pet. Ex. 55, Tab X, at 278. Second, any "mercury efflux disorder" would be genetically based and unlikely to change with age; under the genetically-caused mercury efflux disorder hypothesis, difficulty in excreting mercury in infancy would persist into childhood. In any event, the extremely high difference between the 0.22 µg mean level found in the McDowell study and the mean level of 3.63 µg in Holmes' non-autistic controls strongly suggests that something was wrong with the control samples in the Holmes' study.

One reason for the discrepancy in the control samples could be the methodology for obtaining them. According to the Holmes article, the controls were recruited through appeals to autism parent groups, and the control children and parents were not interviewed in person. Hair samples were mailed directly to the laboratory, making true blinding of samples difficult. In the case of both the controls and the subjects, the hair samples were not obtained under controlled conditions; instead, the investigators relied on parental reports to indicate that the samples represented first baby hair cuts. Holmes, Cedillo Pet. Ex. 55, Tab X, at 278-79.

In 2007, another study of the heavy metal content of hair failed to replicate Holmes' findings.[210] Forty-five children with ASD diagnoses were matched with 45 controls for age, gender, and race/ethnicity. Instead of the striking difference between ASD subjects and controls reported by Holmes, the reported mercury levels were not statistically different between the ASD subjects and controls.

The third study relied upon by Dr. Aposhian was the Adams study, filed as Cedillo Pet. Ex. 82.[211] This study of baby teeth showed mercury levels twice as high in autistic children as in controls. This study appears to contradict the Holmes and Bradstreet studies, which showed lower levels of mercury in autistic children. Doctor Brent also noted an error in the methodology, suggesting that the results were not

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[209] M. McDowell, *et al.*, *Hair Mercury Levels in U.S. Children and Women of Childbearing Age: Reference Range Data from NHANES 1999-2000.* ENVIRON. HEALTH PERSPECT. 112(11): 1165-71 (2004) ["McDowell"].

[210] J. Kern, *et al., Sulfhydryl-Reactive Metals in Autism*, J. TOXICOLOGY ENVIRON. HEALTH 70: 715-21 (2007), filed as Cedillo Res. Ex. L, Tab 34.

[211] J. Adams and J. Romdalvic, *Mercury, Lead, and Zinc in Baby Teeth of Children with Autism Versus Controls,* J. TOXICOLOGY ENVIRON. HEALTH, PART A 70: 1046-51 (2007).

statistically significant, that the studied population was very small, and that, as teeth are not excretory organs, concluding that mercury levels in teeth reflect body burden is highly questionable. Cedillo Tr. at 2467-69.

Both the Holmes and Bradstreet studies have been extensively criticized, and other investigators have failed to replicate their results. The Adams study, even aside from its statistical shortcomings, does not show hypersusceptibility. Weighing the evidence, I conclude that petitioners have failed to demonstrate that children with autism have difficulty excreting mercury, and thus there is no reliable evidence of a mercury efflux disorder or a hypersusceptibility to mercury in children with an ASD diagnosis.

3. The Effects of Methylmercury.

Even if petitioners could establish hypersusceptibility to mercury or a mercury efflux disorder in a subset of children with ASD, petitioners would still have to demonstrate the effects of mercury on the immune system. Unfortunately, most of the evidence of mercury's effects concerns methylmercury, not the ethylmercury into which TCVs are metabolized. A very brief discussion of methylmercury's effects is included here, because of Dr. Aposhian's reliance on studies dealing with methylmercury.

There is ample evidence that methylmercury is toxic at some doses and has more subtle adverse effects at lower doses. It is also well-demonstrated that fetuses and infants are more susceptible than adults to methylmercury's effects.

But, there is no evidence that any level of exposure to methylmercury causes symptoms that mimic those of autism, or that those exposed to mercury are more prone to develop autism.[212] A lengthy article written by Drs. Clarkson and Magos (Clarkson and Magos 2006, Cedillo Pet. Ex. 55, Tab H), summarizes much of the prior research regarding the effects of mercury. They note that in the Iraqi seed wheat disaster, the children who died from prenatal methylmercury exposure showed widespread brain damage, including problems in cell division and in neuronal cell migration. In contrast, infants exposed during the first year of life did not exhibit many adverse effects, even at fairly high blood levels of mercury. *Id*., at 630, 635-36. They concluded that the fetal brain is very sensitive to methylmercury. *Id.*, at 635.

In the Minamata Bay disaster in Japan,[213] children exposed prenatally to high

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[212] Evidence from the Iraqi methylmercury disaster established that the primary toxic effects from its ingestion included central nervous system damage (loss of sensation in hands and feet, paresthesia around the mouth, ataxia, slurred speech, diminution of vision, and loss of hearing). Prenatal exposure resulted in cerebral palsy with mental retardation. Bakir, Cedillo Pet. Ex. 55, Tab D.

[213] *See* T. Tsubaki and K. Irukayama K (Eds.), *Minamata Disease: Methylmercury poisoning in Minamata and Niigata, Japan*, Elsevier, New York (1977), filed as Cedillo Res. Ex. BB, Tab 94. This book exhaustively covers the methylmercury poisoning from contaminated seafood in Japan in the 1950s-70s.

levels of methylmercury developed Minamata disease, a condition similar to cerebral palsy. Cedillo Tr. at 2344. Postnatal exposure showed a different pattern of brain damage. In autopsies of victims, the damage was restricted to specific areas of the brain. The damage was observed in the granule cell layer of the neocerebellum, responsible for the ataxia observed in victims, and in cortical atrophy around the calcarine fissures, responsible for the constriction of visual fields. Clarkson and Magos 2006, Cedillo Res. Ex. 55, Tab H, at 631.

Petitioners relied on Grandjean's Faroe Islands studies (*supra*, n. 187), correlating increased levels of methylmercury in children with subtle defects on some performance tests. Respondent cited the Seychelles Islands studies[214] in response. The Faroe Islands study found some subtle neurological effects associated with higher maternal consumption of whale meat and blubber, but the Seychelles Islands studies did not find similar effects from high fish consumption. Because both studies involved methylmercury ingestion, and there is insufficient information to establish a correlation with ethylmercury's effects, I do not find these studies relevant to inform a discussion about injected thimerosal. I also note that neither the Faroe Islands study nor a New Zealand study[215] demonstrated that methylmercury had any effects similar to autism.

Citing animal studies published in 1975 and 1996, Clarkson and Magos commented that low exposures to methylmercury early in postnatal development may result in immune system deficiencies. However, they did not specify which immune system deficiencies were noted. *See* Clarkson and Magos 2006, Cedillo Pet. Ex. 55, Tab H, at 643.

4. The Effects of Ethylmercury.

Doctors Aposhian and Byers, and the scientific studies they cited, failed to demonstrate that the amount of thimerosal in TCVs can cause immune suppression or the type of brain damage found on brain autopsies of those with ASD. Doctor Aposhian admitted that he was unaware of any human studies reflecting that vaccine levels of

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Congenital disease was observed in children born to victims who were themselves only minimally affected; the symptoms resembled those of cerebral palsy with seizures.

[214] G. Myers, *et al.*, *Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study*, LANCET 361: 1686-92 (2003), filed as Cedillo Pet. Ex. 55, Tab JJ, and P.Davidson, *et al., Effects of Prenatal and Postnatal Methylmercury Exposure From Fish Consumption on Neurodevelopment: Outcomes at 66 Months of Age in the Seychelles Child Development Study*, JAMA 280(8): 701-07 (1998), filed as Cedillo Res. Ex. L, Tab 15.

[215] T. Kjellstrom, *et al., Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 1: Preliminary Tests at Age 4. Report 3080*. Solna, Sweden: National Swedish Environmental Protection Board (1986), filed as Cedillo Pet. Ex. 55, Tab Z, and T. Kjellstrom, *et al., Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 2: Interviews and Psychological Tests at Age 6. Report 3642,* Solna, Sweden: National Swedish Environmental Protection Board (1989), filed as Cedillo Pet. Ex. 55, Tab AA.

thimerosal caused immunosuppression. Cedillo Tr. at 183A. Doctor Fujinami's report noted that, despite extensive study of human exposure to mercury, there is no mention of immunosuppression as a symptom of exposure, nor is there a report of an increase in opportunistic infection after exposure. Cedillo Res. Ex. R at 8.

a. Immune System Effects.

In her somewhat disjointed testimony, and in the slides accompanying that testimony (Cedillo Pet. Tr. Ex. 9), Dr. Byers discussed the effects of mercury on the immune system. This discussion was not included in any substantive way in her expert report. She testified that, in general, mercury produces immune dysregulation. Cedillo Tr. 898. She indicated that mercury affects the ability of DC to function by inhibiting secretion of LPS and proinflammatory cytokines, which impairs the ability of DC to stimulate the adaptive immune system, induces elevated Th2 responses, alters the secretion of IL-6, and produces apoptosis in T cells. According to Dr. Byers, these effects on the immune system may result in a chronic low-grade inflammatory response, which produces autoimmune disease.[216] Cedillo Tr. at 914-16. Doctor Byers was unaware of any research demonstrating that thimerosal affected cytokine production. Cedillo Tr. at 1005-06. She could not cite to any evidence that mercury induced apoptosis in DC. Cedillo Tr. at 1003A.

Doctor Byers was not persuasive. On cross-examination, it became apparent that most of Dr. Byers' testimony on mercury's effects on the immune system came from articles she researched in preparation for trial or from meetings with Dr. Aposhian. Cedillo Tr. at 983A-89. She was unable to answer questions regarding the species of mercury that produced the types of immune system effects cited in her slide presentation. Although much of her trial testimony concerned the effects of mercury on the immune system, she devoted only one paragraph of her expert report to those effects. Cedillo Tr. at 983, 987A-90; Cedillo Pet. Ex. 57 at 4-5. She misstated the amount of mercury Michelle Cedillo received from her vaccinations, confusing the amount of thimerosal with the amount of mercury. Cedillo Tr. at 903, 909-12. Although petitioners' counsel took responsibility for the error appearing in Cedillo Pet. Tr. Ex. 9 at 17, the context of the testimony suggests that Dr. Byers was either testifying from a document that she had not prepared or understood, or was simply confused about the amount of mercury in thimerosal. In either event, her frequent deferrals to Dr. Kennedy, Dr. Kinsbourne, and Dr. Aposhian, suggest that she was offering testimony outside her expertise. *See, e.g.*, Cedillo Tr. at 894 (deferring to Dr. Aposhian "for most of the mercury stuff"), 896A, 898, 912, 924, and 978A. When asked to summarize the effect of mercury on the immune system, she responded: "I would say that the most important thing that we should now be concerned with is the effect of thimerosal on the ability of

[216] Mercury chloride induces a form of autoimmunity in animals, and possibly in humans. Clarkson and Magos 2006, Cedillo Pet. Ex. 55, Tab H, at 616. However, there is no evidence that ethyl or methylmercury induce the same effect, and no evidence that ASD in general, and regressive autism in particular, are autoimmune conditions.

dendritic cells to behave in a normal fashion so that they can clear viruses." Cedillo Tr. at 913. However, according to Dr. McCusker, the primary function of dendritic cells is not to "clear viruses." They present antigens to B and T cells to activate them. The B and T cells then inactivate viruses in transit or kill the cells that harbor them. Cedillo Tr. at 2231A-33A. Doctor Byers also testified that mercury "impacts on the secretion of LPS." Cedillo Tr. at 914. However, LPS is secreted by bacteria, not by the immune system. Cedillo Tr. at 1006; 2234A.

Doctors Aposhian and Byers relied primarily upon two studies to demonstrate mercury's effects on immune system cells, extrapolating effects from *in vitro* or animal studies to predict *in vivo* effects on humans. Doctor Byers conceded that many of the *in vitro* studies on the effects of mercury on immune response failed to identify the dose of mercury necessary to establish the effects, but testified that the Goth[217] and Agrawal studies[218] involved doses of thimerosal similar to, or less than, those found in vaccines. Cedillo Tr. at 897A, 902A-03. According to Dr. Byers, the Goth study demonstrated that 20 µg of thimerosal caused abnormal IL-6 production in mouse (murine) DC, and the Agrawal study showed that 25 µg of thimerosal caused abnormal IL-6 production in human DC *in vitro*. Cedillo Tr. at 902A-03; Cedillo Pet. Tr. Ex. 9 at 16. She provided no evidence that altered IL-6 production, or any other observed alteration in immune cells, would have any effect on viral clearance or would cause damage to glial cells.

The Goth study examined the effects of various concentrations of thimerosal and ethylmercury on murine DC in culture. The highest concentrations killed more than 90% of the DC, probably by inducing apoptosis. Not surprisingly, their viability was dose-dependent. The authors stated that a practical application of their findings was identifying DC as sensitive targets for ethylmercury mediated dysfunction. They indicated that thimerosal and ethylmercury should be considered in assessing contributions to altered immune functioning. Goth, Cedillo Pet. Ex. 55, Tab Q, at 1090. In essence, they suggested that when immune dysfunction was found, ethylmercury should be considered as a possible cause.

The Agrawal study looked at the *in vitro* effects of thimerosal on human DC. The cells were cultured with thimerosal for six-eight hours, then stimulated with LPS and then cultured with thimerosal for another 18-20 hours, and several different types of responses were measured. At a 50 nanomolar thimerosal concentration, the cells shifted to a Th 2 function, which is an anti-inflammatory and pro-allergy response. This effect was not seen at a 10 nanomolar concentration. Cedillo Tr. at 2331-32; Cedillo Res. Tr. Ex. 17 at 13-15. Thimerosal alone did not suppress cytokine production, but with LPS stimulation, thimerosal suppressed the secretion of pro-inflammatory

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[217] S. Goth, *et al.*, *Uncoupling of ATP-mediated Calcium Signaling and dysregulated interleukin-6 Secretion in Dendritic Cells by Nanomolar Thimerosal,* ENVIRON. HEALTH PERSPECT. 114(7): 1083-91 (2006) ["Goth"], filed as Cedillo Pet. Ex. 55, Tab Q.

[218] Agrawal, Cedillo Pet. Ex. 55, Tab A.

cytokines IL-6 and TFN-α. It also suppressed secretion of Th1 cytokines such as IL-12. It did not affect the secretion of IL-10. Thimerosal had no effect on the ability of DC to induce T cell proliferation. The concentrations of thimerosal involved did not induce apoptosis in DC or affect their maturation. Agrawal, Cedillo Pet. Ex. 55, Tab A, at 476.

Doctor Brent testified that mercury can affect the immune system in many different ways, but that there are no studies that demonstrate any adverse effect of vaccine dose levels of thimerosal on the human immune system. Cedillo Tr. at 2334-35, 2438. He criticized the reliance of Drs. Aposhian and Byers on the Goth and Agrawal articles. He commented: "I think there's no reasonable way anybody could conclude from the Goth and Agrawal studies that the thimerosal from the vaccine would cause immunosuppression." Cedillo Tr. at 2325. As he pointed out, the Goth article discussed an *in vitro* study of a rare type of mouse dendritic cell, not human cells. And, as Drs. Brent and McCusker both testified, the mouse immune system is different from that of humans. Cedillo Tr. at 2325, 2227A.

Doctor McCabe provided additional insights into the significance of the Goth study. He testified that thimerosal's ability to provoke changes in intercellular calcium *in vitro* is well established, and that the Goth study demonstrated that it also does so in DC. The study showed that thimerosal reduced IL-6 production. It did not demonstrate an effect on physiologic or immunologic function from the lower IL-6 levels. Snyder Tr. at 754A-55. He described the Goth study as linking A to B, and Dr. Byers' interpretation of that study as moving from A to B to Z, while skipping all the steps in between. Snyder Tr. at 755-56.

Subjecting cells in culture to ethylmercury does not mimic what happens to ethylmercury in the human body. Cultured cells are not afforded the protection of other body systems. Proteins such as metallothionein, glutathione, and cysteine, which inactivate mercury, are not present in cell cultures. *In vivo*, mercury is transported to the tissues via red blood cells, and much of the mercury remains bound to those blood cells. These blood cells are not present when mercury is applied directly to cells in culture. For these reasons, cells in culture are far more vulnerable, and levels of substances which would not cause injury *in vivo* will kill cultured cells. Cedillo Tr. at 2321-23; Cedillo Pet. Ex. 55, Tab H, at 629.

Both studies involved the exposure of cells to thimerosal. Most cells in the body are not exposed to thimerosal after receipt of TCVs because thimerosal rapidly breaks down into ethylmercury. Thus, any findings regarding thimerosal exposure are not relevant to the effects of TCVs because after administration of a TCV, the vast majority of human cells are exposed to ethylmercury, not thimerosal.

According to Dr. Brent, Dr. Aposhian was incorrect when he testified that the concentrations of thimerosal used in the Goth study equaled TCV-level exposures. The 100 nanomolar level of thimerosal at which a cellular effect was shown is the equivalent of about 20 µg/L of mercury exposure. However, in the body, the mercury has to be

unbound to act on cells, and about 90% of the ethylmercury administered is bound to red blood cells, leaving only 10% free to act on cells. Some of that 10% is also bound to proteins and not available to act on cells. Thus, an exposure to 20 µg/L in cell culture is the equivalent of greater than 200 µg/L of blood mercury. Whole blood levels of 200 µg/L are very high levels, and far higher than any child would have after administration of a TCV.[219] Cedillo Tr. at 2326-29A; Cedillo Res. Tr. Ex. 17 at 8-12. Further, the Goth study does not address the duration of the effects from exposure. Because the half-life of ethylmercury in the blood is approximately 8 days (Cedillo Tr. at 2330), a substantial portion of the mercury administered would be eliminated through urine or feces, and thus not available to act on cells.

Doctor Brent offered a similar criticism of the Agrawal article. The 50 nanomolar level, at which effects were seen, would be equivalent to a blood mercury level of 10 µg/L, 90% of which would be bound to red blood cells. In order to get DC exposed to 10 µg/L, the whole blood level of mercury would have to be at 100 µg/L. Thus, the cultured human DC were exposed to far greater levels of thimerosal than human infants would be when vaccinated with TCVs. Cedillo Tr. at 2331-32; Cedillo Res. Tr. Ex. 17 at 13-15. The Agrawal study did not address whether the exposure would have any long lasting effect or might impact the body's ability to clear measles virus. Cedillo Tr. at 2332-33.

Doctor McCusker interpreted the Agrawal paper differently than Dr. Byers did. The human DC treated with thimerosal were stimulated with LPS. One result was a decreased production of IL-6. IL-6 is associated with fever; downregulated (reduced production of) IL-6 would reduce the likelihood of a fever, meaning there would be less inflammation as the result of thimerosal treatment, not more. Cedillo Tr. at 2234A-35A.

Doctor Brent was cross-examined about two articles by Shenker, *et al.*, Cedillo Pet. Ex. 55, Tab DDD[220] and Cedillo Pet. Ex. 55, Tab EEE.[221] As Dr. Brent noted, the Shenker 1992b study[222] involved mercuric chloride, a species of mercury different from

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[219] *See* T. Stajich, *et al., Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants,* PEDIATRICS 136(5): 679-81 (2000), filed as Cedillo Pet. Ex. 55, Tab QQ (finding the highest blood mercury level in a preterm infant 48-72 hours after vaccination to be 23.6 µg/L, with the mean level at 7.36 µg/L).

[220] B. Shenker, *et al.*, *Immunotoxic Effects of Mercuric Compounds on Human Lymphocytes and Monocytes. I. Suppression of T-cell Activation*, IMMUNOPHARMACOL. IMMUNOTOXICOL. 14(3): 539-53 (1992) ["Shenker 1992a"].

[221] B. Shenker, *et al.*, *Immunotoxic Effects of Mercuric Compounds on Human Lymphocytes and Monocytes. II. Alterations in Cell Viability*, IMMUNOPHARMACOL. IMMUNOTOXICOL. 14(3): 555-77 (1992) ["Shenker 1992b"].

[222] The cross-examination concerned a reference to this study found in K. Pollard and P. Hultman. MERCURY AND THE IMMUNE SYSTEM, Chapter 14, "Effects of Mercury on the Immune System," at 421-40 (publication date not provided), filed as Cedillo Pet. Ex. 81.

that contained in vaccines, and much higher doses of mercury than would be found in vaccines. Cedillo Tr. at 2441. Doctor Brent acknowledged that extremely small amounts of thimerosal in TCVs will be converted to mercuric mercury (also known as inorganic mercury), but that the amounts showing effects on monocytes and B and T cells in this study were far higher than would be found after vaccination. Cedillo Tr. at 2443. The Shenker 1992a study involved the effects of species of mercury other than ethylmercury (methyl mercury chloride and mercury chloride), on T cell proliferation. It also involved doses higher than those contained in vaccines. Thus, neither study is particularly helpful in demonstrating even possible, much less probable, immune system effects from the levels of thimerosal found in vaccines. As Doctor Brent testified: "[i]f you want to enlighten this discussion in the true scientific fashion about what happened with ethylmercury at doses associated with vaccines then we should discuss literature on ethylmercury at exposures we see with the vaccine. Now, I don't think were going to have that discussion and the reason being there are no papers that show any adverse effects." Cedillo Tr. at 2453.

Another study relied upon by Dr. Byers was the Hornig study,[223] which demonstrated that autoimmune disease-sensitive mice exposed to thimerosal showed growth delay and other changes, while mice strains with resistance to autoimmunity were not affected. The affected mice also exhibited alterations at the neuronal cell level, and showed densely packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters. Clarkson and Magos discussed this study in their 2006 article. Cedillo Pet. Ex. 55, Tab H, at 647. They noted that the dosing schedule did not mimic the infant vaccination schedule because it did not allow for clearance times. Because the effects were seen only in highly inbred mice, this study is even more limited than most animal studies.

Although one study demonstrated some association with gastrointestinal symptoms in autism and families with a history of autoimmune disorders,[224] the difference between children with ASD and typically developing children in the study was small. Leaving aside the problems in extrapolating from animal studies to human effects, the small association between a possible genetic predisposition to autoimmune disorders and autism is too small to render this study relevant to the role of mercury in immune system malfunctions.

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[223] M. Hornig, *et al.*, *Neurotoxic effects of postnatal thimerosal are mouse strain dependent,* MOL. PSYCHIATRY June; 1-13 (2004) at 1, filed as Petitioners Omnibus Ex. 86. The Petitioners' Omnibus exhibits were not filed into the record of any of the three Theory 1 test cases; they were filed by the PSC in the OAP prior to any test case being designated. Because Dr. Byers relied upon this article, which was discussed in other exhibits that were filed, I have read it to aid in evaluating Dr. Byers' testimony.

[224] *See* M. Vallicenti-McDermott, *et al. Frequency of Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders and Association with Family History of Autoimmune Disease*, DEVEL. BEHAV. PEDIATRICS 27(2): 128-36 (2006) ["Vallicenti-McDermott"], filed as Cedillo Pet. Ex. 61, Tab HHHH. This cross-sectional study examined the association of gastrointestinal symptoms with a family with a history of autoimmune disease. A family history of autoimmune disease was reported in 38% of children with ASD, as compared to 34% of controls.

Doctor Byers testified that, *in vitro*, mercury inhibits neutrophil function. Neutrophils are a part of the immune system that kill by using an oxidative burst. Mercury inhibits the oxidative burst capacity of these cells. Cedillo Tr. at 895.

Doctor McCabe challenged Dr. Byers' testimony that mercury targets T regulatory cells (Cedillo Tr. at 897A), testifying that if there were any literature supporting that statement, he would be aware of it. Snyder Tr. at 749A. He also challenged her testimony that mercury-induced autoimmunity in animal models would demonstrate a similar impact on the human immune system. The amounts of mercury given to mice in the studies that he examined would be approximately 1,000 times the amount of mercury in TCVs. Snyder Tr. at 752-53.

It is clear that mercury has some effects on immune system cells. Doctor Brent acknowledged that monocytes appear to be the most sensitive to mercury's effects, followed by B cells and then T cells. However, there is insufficient evidence to conclude that vaccine level doses of ethylmercury have any effects on the immune system, *in vivo*, much less that they suppress its functioning. Cedillo Tr. at 2443.

b. Central Nervous System Effects.

Doctor Aposhian's report stated that mercury can cause injury to the human embryo[225] and infant central nervous system.[226] Cedillo Pet. Ex. 55 at 2. Mercury can have significant effects on brain development, but there is no evidence of injury from the levels of ethylmercury associated with vaccine exposure. Doctor Brent noted that mercury is a naturally occurring substance to which we are all exposed, and that the body has evolved very sophisticated mechanisms to inactivate the mercury that accumulates in our brains. Adverse effects are observed only when those mechanisms are overwhelmed. Cedillo Tr. at 2473-74.

Mercury's effects on the developing brain were also discussed by Doctor Rust. He testified that intrauterine mercury exposure results in what is called a static encephalopathy,[227] a condition very different from autism. Mercury exposure causes injury to the visual and auditory cortexes, but spares large neurons. In autism, the large

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[225] To the extent, if any, that TCVs affect human embryos, the effects would be from vaccinations administered to the mother. That was not a theory presented in any of the Theory 1 test cases.

[226] Doctor Aposhian also stated that any form of mercury entering the brain is converted to mercuric mercury (inorganic mercury). This was an overstatement. Some of any form of mercury that enters the brain is converted into inorganic mercury; the amount varies by the species of mercury involved.

[227] The term "encephalopathy" can be applied to any degenerative disease of the brain. DORLAND'S at 610–11. A static encephalopathy is one that is not changing. The general definition of an ecephalopathy should not be confused with the Vaccine Injury Table's more restrictive definition. *See* 42 C.F.R. § 100.3(b)(2).

neurons are injured, and the small neurons are spared. Brain injuries from mercury exposure do not present with the same clinical appearance as with autism. Hazlehurst Tr. at 464A-65A; 496A-97A. Mercury exposure damages the inner white matter and deeper cortical laminae. Autism shows an opposite pattern, with the outer white matter as the site of injury. Mercury exposure spares the Purkinje cells; in autism, there is a significant loss of Purkinje cells. Hazlehurst Tr. at 497A. It does not appear that mercury targets or affects the brain's innate immune system, the microglia.

5. Conclusions on the Mercury Aspect of Theory 1.

I conclude that petitioners have demonstrated that ethylmercury can harm the immune system, but have failed to show that it does so in the amounts contained in TCVs. Even if mercury were shown to have damaged the immune systems of children with ASD, petitioners have not accounted for the probable contribution of environmental mercury from sources other than TCVs. *See* Cedillo Pet. Tr. Ex. 1 at 11 (Dr. Aposhian's estimates of average daily intake of mercury from sources other than TCVs). Petitioners have failed to demonstrate the existence of mercury efflux disorders or a hypersusceptibility of some children with autism to mercury's effects. They have failed to show that mercury's effects on the brain resemble the pathophysiology found in autism or to show that TCV-levels of mercury affect microglia, the brain's innate immune system cells.

Section VI. The Measles Theory.

The MMR vaccine is usually administered to children in the U.S. between 12-15 months of age,[228] shortly before parents first begin to notice the behavioral symptoms that eventually lead to their children's ASD diagnoses. It is not surprising that some parents considered the vaccine to be causal. The 1998 publication of a paper[229] suggesting a temporal relationship, and implying a causal one, between the MMR vaccine and onset of autistic symptoms in a group of 12 children being treated for gastrointestinal complaints–a symptom not uncommon in autistic children–added fuel to smoldering suspicion. The paper's primary author, Dr. Andrew Wakefield, later advanced a hypothesis as to how measles virus could cause both the gastrointestinal complaints and autism. Although Dr. Wakefield's hypothesis differs in some respects from the theories advanced in this case, petitioners' theories are its linear descendants. Some discussion of how the measles hypothesis arose, and how it changed, is helpful in evaluating petitioners' MMR theory of causation.

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[228] *See* F. DeStefano, *et al., Age at First Measles-Mumps-Rubella Vaccination in Children with Autism and School-Matched Control Subjects: a Population-Based Study in Metropolitan Atlanta*, PEDIATRICS 113(2): 259-66 (2004) ["DeStefano"], filed as Cedillo Res. Ex. P, Tab 38.

[229] A. Wakefield, *et al.*, *Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive developmental disorder in children*, LANCET 351: 637-41 (1998) ["Wakefield 1998"], filed as Cedillo Res. Ex. R, Tab 23.

The medical theory connecting measles vaccine virus with ASDs was provided by the testimony of Dr. Kinsbourne.[230] His hypothesis was that, due to an ineffective immune response, some children with regressive autism are unable to clear the measles vaccine virus from their bodies. The virus inhabits the gut,[231] and is transported by macrophages through the circulatory system to the brain. After crossing the blood-brain barrier, the virus invades the astroglia, neurons, and possibly microglia, invoking a response by the brain's innate immune system, the microglia. The microglia produce proinflammatory cytokines, causing brain inflammation. This inflammation disorganizes critical circuits in the brain, interrupting communication among various areas of the brain. These disorganized circuits manifest in autistic symptoms. Cedillo Tr. at 1092A-95.

Alternatively, or additionally, under Dr. Kinsbourne's theories, the immune response to the measles virus caused gliosis, or scarring, of astrocytes (a type of glial cell sometimes referred to as astroglia). One function of astrocytes is to mop up excess glutamate at the synapses, the bridges between neurons. Damaged or destroyed astrocytes may not perform this function properly, resulting in over-activation of the brain. Excess glutamate, the brain's most prevalent excitatory neurotransmitter, can kill neurons and can cause an imbalance between excitatory and inhibitory neurotransmitters. Cedillo Tr. at 1094-1095, 1097-1100, 1148A-52A.

Both theories rely upon a link between gut disorders in autistic children ("autistic enterocolitis"[232]) and the presence of measles virus genomic material in their gut tissue. Doctor Kinsbourne's hypotheses rested upon findings of measles virus genomic material in the gut tissue and CSF of more autistic children than in similar samples taken from typically developing children, at a time long after the virus should have cleared the body. Cedillo Tr. at 1180A-1183A. The evidence supporting the presence of measles virus in the gut tissue was provided primarily by Dr. Wakefield's research and by the testing performed at Unigenetics laboratory. This finding is a necessary condition for the logical connection between autism and the measles virus; absent the presence of measles virus genomic material, Dr. Kinsbourne would not opine that a

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[230] Doctor Kennedy provided much of petitioner's evidence on measles virus, but as petitioners' witnesses conceded, based on limitations in his background, training, and experience, he was not qualified to provide the theory of causation. *See* Snyder Tr. at 432A-32B (Dr. Kennedy deferring to Dr. Kinsbourne for any testimony on how measles virus could cause autism, stating that his own "knowledge of autism is very limited,") and Dr. Byers' testimony indicating that she and Dr. Kennedy did not have the qualifications to say that MMR causes ASD. Cedillo Tr. at 947.

[231] Doctor Krigsman provided most of the information on gut disorders in autistic children, but it was Dr. Kinsbourne who linked the gut disorders and autism through this biologic process.

[232] Although there was ample evidence that "autistic enterocolitis" is not recognized as a distinct medical condition (*see, e.g.*, testimony of Dr. Hanauer at Cedillo Tr. 2143; testimony of Dr. MacDonald, Hazlehurst Tr. at 662A-63), I use the term to discuss the theories advanced by petitioners. My use of this term should not be construed as a determination that the gut symptoms in those with ASD constitute a new disease process or a separate autism phenotype recognized by the medical community.

child's autism was caused by the MMR vaccine. As he testified: "I would not give an opinion on a case that did not have a positive biopsy...nor would I give an opinion if there was no reason to even think of measles. I wouldn't then say it was measles." Cedillo Tr. at 1180A.

Respondent mounted a vigorous challenge to the scientific validity of reports of measles virus genomic material in autistic children in addition to challenging the biological plausibility of, and the logical connection between, the theories. Challenging the scientific validity both of Dr. Wakefield's research and Unigenetics' testing, respondent relied upon experts in many disciplines.

This section begins with a discussion of how the MMR theory first arose, followed by a more detailed explication of the current theory. The discussion of "autistic enterocolitis" is followed by the evidence concerning the wild strain measles virus, covering how the vaccine strain of the virus differs from the wild-type virus, their particular effects on the immune system, and the diseases commonly recognized as being caused by the virus strains. Finally, this section examines PCR testing, problems commonly encountered in such testing, and the problems demonstrated in the Unigenetics testing program in particular. I postpone a discussion of the testing specific to Colten until Section VIII.

A. The Genesis and Mutation of the Measles Theory of Autism Causation.

1. The Wakefield Hypotheses.[233]

The original hypothesis connecting MMR vaccine and autism grew out of work by Dr. Andrew Wakefield in the U.K.[234] A number of gastrointestinal diseases and

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[233] Much of this section is drawn from the testimony of Dr. MacDonald in *Hazlehurst.* Doctor MacDonald testified that he was very familiar with the investigations of Dr. Wakefield's claims. Hazlehurst Tr. at 650A.

[234] Petitioners resisted respondent's efforts to focus some of respondent's experts' testimony on problems with Dr. Wakefield's hypotheses and research. During opening statements in *Snyder*, petitioners' counsel characterized respondent's evidence regarding Dr. Wakefield as a "smear campaign." Snyder Tr. at 24. I found the testimony and exhibits pertaining to Dr. Wakefield to be highly relevant for several reasons. First, Dr. Wakefield is responsible for much of the research supporting the autistic enterocolitis theory, relied upon by Dr. Kinsbourne, proposing vaccine causation in those children with the postulated "regressive autistic enterocolitis" phenotype. Second, the validity of specific tests for measles viral material in gut tissue performed by the Unigenetics laboratory is critical to Dr. Kinsbourne's theory. Doctor Wakefield was a co-author of the paper reporting the testing performed by Unigenetics, and the primary author or co-author of numerous journal articles filed as evidence in the Theory 1 cases. Doctor Wakefield was, at one time, the Director of Research for the International Child Development Resource Center, a nonprofit corporation created by Colten's treating physician, Dr. Bradstreet. Snyder Tr. at 254-55. Finally, Dr. Wakefield filed a "commentary" (Snyder Pet. Ex. 27), on Dr. Ward's supplemental report in *Snyde*r (Snyder Res. Ex. M); thus, Dr. Wakefield provided evidence in this case. As such, his scientific methodology and theories, and the validity of the research supporting them, are fair game for criticism.

conditions are discussed in this section. Crohn's disease[235] and ulcerative colitis[236] are chronic inflammatory diseases of the intestines. Both diseases are considered idiopathic, meaning that they have no commonly recognized cause. Cedillo Tr. at 2089.

Inflammatory bowel disease ["IBD"] is a term encompassing a number of disorders of the digestive tract, including ulcerative colitis, indeterminate colitis, nonspecific colitis, microscopic colitis, and Crohn's disease. Cedillo Tr. at 428, 2088A. As the name suggests, inflammation is a hallmark of all IBD. Cedillo Tr. at 2089. Anything that produces inflammation in the digestive tract would be classed as an IBD.[237] Cedillo Tr. at 2088A-89. In contrast, irritable bowel syndrome ["IBS"] is a symptomatic disorder affecting the digestive tract, related to increased motility. It presents with symptoms of abdominal pain with diarrhea or constipation or, most commonly, with alternating diarrhea and constipation. Cedillo Tr. at 2089-90A. It does not progress to IBD, colitis, or Crohn's disease. Cedillo Tr. at 2167, 2190A.

a. Measles and Crohn's Disease.

In 1993, building on an earlier hypothesis, Dr. Wakefield postulated in a journal article that Crohn's disease was caused by infarctions of small blood vessels in the gut wall and that the measles virus was responsible for the infarctions.[238] The journal article received a great deal of media attention, but critical review found a number of deficiencies in the study.[239]

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[235] Crohn's disease is a chronic inflammatory disease that may occur in any part of the gastrointestinal tract from the mouth to the anus, but, most commonly, it involves the terminal ileum. It may involve the lining of the bowel, but may also penetrate the wall of the bowel itself. It may be patchy, with some areas of the bowel affected and others normal in appearance. In Crohn's disease, granulomas, fistulas, or strictures are very common. DORLAND'S at 531; Cedillo Tr. at 429A-31A. Granuloma in tissue is considered one of the pathological markers of Crohn's disease. D. Robertson and R. Sandler, *Measles Virus and Crohn's Disease: A Critical Appraisal of the Current Literature*, INFLAMM. BOWEL DIS. 7(1): 51-57 (2001), filed as Snyder Res. Ex. M, Tab 11. The ileum is the distal portion of the small intestine, which ends at the cecum, the beginning of the colon. DORLAND'S at 907.

[236] Colitis is inflammation of the colon (the large intestine). In ulcerative colitis, inflammation is generally limited to the lining of the colon, without deep penetration into the muscular layer of the bowel. The inflammation begins at the anus and extends back into the colon in a contiguous pattern. It may involve only a portion of the rectum or extend to the entire colon. Cedillo Tr. at 429A-31A, 2088A-89.

[237] Inflammation can be caused by infections with various pathogens, such as salmonella or rotavirus, or by radiation or the use of nonsteroidal anti-inflammatory drugs. Cedillo Tr. at 2088A-89.

[238] M. Smith and A. Wakefield, *Viral Association with Crohn's Disease*, ANN. MED. 25(6): 557-61 (1993), filed as Cedillo Res. Ex. BB, Tab 89.

[239] *See, e.g.*, M. Afzal, *et al.*, *Measles virus and Crohn's disease*, GUT June; 44(6): 896-97 (1999), filed as Cedillo Res. Ex. BB, Tab 2; M. Iizuka, *et al., Absence of measles virus in Crohn's disease,* LANCET 345: 199 (1995), filed as Cedillo Res. Ex. BB, Tab 46 ["Iizuka1995"]; J. Hermon-Taylor *et al.*, *Measles virus and Crohn's disease*, LANCET 345: 922-23 (1995), filed as Cedillo Res. Ex. BB, Tab 43 (a letter to the editor of LANCET, with a chart reflecting the lack of any association between Crohn's disease and either

Gut tissue was relatively uncharted territory with regard to searches for measles virus. Prior to the development of Dr. Wakefield's hypothesis, there had been no widespread effort to look for measles virus in gut tissue.[240] Measles researchers believed that measles virus was entirely cleared from the body of those who survived measles disease, except in the very rare diseases discussed later in this section.

Because there were no studies to detect measles virus in gut tissue before Dr. Wakefield's research, two steps were necessary to develop evidence that measles virus might cause gut disorders. First, Dr. Wakefield and his team needed to establish the presence of persistent measles virus in gut tissue. If present, they still needed to establish that its presence was abnormal and associated with a disease process. To do so, they needed to show that it was present significantly more often in those with gastrointestinal disorders than in those without such disorders. They failed on both accounts.

Doctor Wakefield published other papers, in 1995[241] and 1997,[242] stating that measles virus causes Crohn's disease. Concerns developed about Dr. Wakefield's claims when a French researcher noted that the antibody Dr. Wakefield used to identify measles virus reacted with all tissues, not just inflamed bowel tissue. A Japanese research group used PCR techniques on tissue samples from Crohn's disease patients, and was also unable to detect the virus.[243] A Japanese research group also examined the second antibody Dr. Wakefield used to detect measles virus, and the researchers

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wild-type measles infections or the introduction of the MMR vaccine); and Snyder Res. Ex. M, Tab 11, at 52 (noting that four groups were unable to isolate measles virus RNA from Crohn's disease patients' gut tissue, and that the antigen initially identified by Wakefield was a host protein that mimics measles virus immunohistochemically).

[240] J. Fournier, *et al.*, *Subacute sclerosing panencephalitis: detection of measles virus RNA in appendix lymphoid tissue before clinical signs*, BRITISH MED. J. 293: 523-24 (1986), filed as Cedillo Pet. Ex. 61, Tab X. This case report noted the presence of measles virus in a child's appendix eight years after her measles infection. The child was diagnosed with subacute sclerosing panencephalitis ["SSPE"] shortly thereafter, with onset of the disease 15 days after the appendectomy. One exhibit mentioned other studies involving the detection of measles virus in tissue removed during appendectomies. *See* J. Bullowa, *et. al.*, *Acute Appendicitis in the Exanthems*, AM. J. DIS. CHILD. 53: 1029-38 (1936), at 1031, filed as Cedillo Res. Ex. V, Tab 12 (discussing studies finding giant cells in lymphoid tissue of the appendix in patients undergoing appendectomy during active measles disease).

[241] A. Wakefield, *et al., Crohn's Disease: Pathogenesis and Persistent Measles Virus Infection*, GASTROENTEROLOGY 108(3): 911-16 (1995), filed as Cedillo Res. Ex. BB, Tab 96.

[242] This paper was apparently not filed as an exhibit in this case, although it was discussed by Dr. MacDonald during his testimony in *Hazlehurst*.

[243] Y. Haga, *et al., Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction*, GUT 38(2): 211-15 (1996), filed as Cedillo Res. Ex. BB, Tab 41. *See also* Iizuka, Cedillo Res. Ex. BB, Tab 46 (a letter briefly describing unsuccessful efforts to find the measles virus N, M, H, or F genes in gut tissue).

determined that it was reacting with a human protein.[244] These reports were followed by a number of articles, published from 1996-2000, demonstrating that the measles virus was not present in Crohn's disease. In 1998, Dr. Wakefield appeared as the senior researcher on an article describing Dr. Nicholas Chadwick's unsuccessful attempts to find the measles virus in the gut tissue of Crohn's disease patients.[245] Hazlehurst Tr. at 632A-34A. Why Dr. Wakefield appeared as an author on an article casting doubt on his claims of measles virus involvement in Crohn's disease is unclear.

b. Doctor Wakefield's "Autistic Enterocolitis" Hypothesis.

In 1998, Dr. Wakefield published a paper in *Lancet* describing 12 autistic children with symptoms of abdominal pain and food intolerance.[246] During colonoscopies on the children, Dr. Wakefield found lymphonodular hyperplasia ["LNH"] in their small intestines (a finding often referred to as ileal lymphonodular hyperplasia ["ILNH"][247] and mild nonspecific colitis. Doctor MacDonald characterized this paper as "probably the worst paper that's ever been published in the history of [*Lancet*]." Hazlehurst Tr. at 633A-34A. Ten of the paper's 12 authors later filed a "Retraction of an Interpretation" of the paper.[248]

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[244] M. Iizuka, *et al., Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease,* GUT 46: 163-69 (2000) ["Iizuka 200"], Cedillo Res. Ex. BB, Tab 45 (finding that the measles related antigen found in the intestine of Crohn's disease patients was derived from human protein, not measles virus).

[245] Doctor MacDonald referred to Dr. Wakefield's "graduate student" in his testimony. This graduate student was Dr. Chadwick, whose article, N. Chadwick, *et al., Measles Virus RNA Is Not Detected in Inflammatory Bowel Disease Using Hybrid Capture and Reverse Transcription Followed by the Polymerase Chain Reaction*, J. MED. VIROL. 55(4): 305-11 (1998), was filed as Cedillo Res. Ex. BB, Tab 103. Doctor Wakefield was listed as the senior researcher on this article. Doctor Chadwick testified that he began working for Dr. Wakefield in 1994. He began testing tissue and blood samples from autistic children in 1996 for the presence of measles virus RNA. Nine of the samples initially tested positive for the presence of measles virus, but confirmatory gene sequencing at another laboratory demonstrated that all of these results were false positives. Cedillo Tr. at 2283-89A. He informed Dr. Wakefield of these negative results. Cedillo Tr. at 2286-87. Doctor Chadwick's declaration, filed as Cedillo Res. Ex. QQ, contained more detail regarding this conversation. He stated that he had earlier informed Dr. Wakefield of the negative PCR tests for measles virus, and specifically asked not to be included on the list of authors for publication because of the negative results. *Id*., at 4; *See also* Cedillo Tr. at 2289A-90A.

[246] Wakefield 1998, Cedillo Res. Ex. R, Tab 23.

[247] ILNH is an enlargement of the lymph nodes in the small intestine and colon. Hazlehurst Tr. at 616A. Lymphonodular hyperplasia is characterized by small nodules present below the mucosal level in the colon, formed by the B lymphocytes coalescing to form a nodule. Lymphoid nodules are part of the immune system of the bowel. When the B lymphocytes are stimulated by foreign tissue, the B cells reproduce and the underlying lymphoid nodule grows larger. Cedillo Tr. 445A-47.

[248] *See* S. Murch, *et al., Retraction of an interpretation,* LANCET 363: 750 (2004), filed as Cedillo Res. Ex. P, Tab 114.

This 1998 *Lancet* publication was accompanied by another news conference suggesting that the gut findings were caused by the MMR vaccine. This connection was based on parental reports that the gut symptoms that prompted the colonoscopies occurred within days after the MMR vaccination.[249] Hazlehurst Tr. at 636A-37A. Doctor Wakefield hypothesized that the mumps and rubella components of the MMR vaccine interfered with the immune response to the measles component of the vaccine, allowing the measles virus to persist in the gastrointestinal tract. The measles virus caused gut inflammation, causing ILNH, which resulted in a "leaky gut." The leaky gut allowed opioid peptides, products of digestion, to pass through the gut wall and into the bloodstream. Once in the bloodstream, they traveled to the developing brain and caused autism. Hazlehurst Tr. at 641A.

A 2002 paper by Wakefield[250] described a larger study of 48 autistic patients, in addition to the original 12, with 37 control patients. The study focused on large lymphoid follicles in the ileum and symptoms of nonspecific colitis, and purportedly found enterocolitis of both the ileum and the colon in the autistic patients. For purposes of Dr. Wakefield's theory, the inflammation had to be present somewhere in the small intestine in order for the opioid peptides to pass into the bloodstream. Because the colon does not digest food, inflammation found only in the colon could not be the source of opioid peptides. Hazlehurst Tr. at 644-46A, 663-64. The co-occurring conditions of gut inflammation and autism described by Dr. Wakefield and his co-authors became known as "autistic enterocolitis."[251] Hazlehurst Tr. at 629A-30A, 674A; Cedillo Tr. at 1415A-19A.

c. Criticism of the Wakefield Hypotheses.

Respondent's witnesses were highly critical of Dr. Wakefield's hypothesis, and of Dr. Wakefield personally. Doctors MacDonald and Fombonne were both part of a U.K. Medical Research Council investigation into Dr. Wakefield's claims. Doctor MacDonald found evidence suggesting fraud. Doctor Rima examined some of the evidence Dr. Wakefield relied upon and found that it was not what Dr. Wakefield claimed it to be.

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[249] Doctor Fombonne noted that Dr. Wakefield appeared to date the onset of autistic symptoms within days of vaccination, which was contrary to the experience of clinicians diagnosing autism. Most clinicians note that parental concerns develop gradually over a period of months. Cedillo Tr. at 1286A. The questionnaire used in parent interviews by most clinicians asks about the child's age in months, because experience has shown that parents really cannot date the onset of symptoms more closely than that. Cedillo Tr. at 1286A-1287A.

[250] A. Wakefield, *et al.*, *Enterocolitis in Children with Developmental Disorders,* AM. J. GASTROENTEROL. 95: 2285-95 (2000), filed as Cedillo Pet. Ex. 61, Tab NNN ["Wakefield 2002"].

[251] In the context of the Theory 1 test cases, the term "autistic enterocolitis" was applied to a postulated phenotype of regressive autism, descriptive of children who experienced autistic regression shortly after administration of the MMR vaccination, and whose condition included gastrointestinal symptoms suggestive of the bowel disease Dr. Wakefield called ILNH. Hazlehurst Tr. at 629A-30A, 674A; Cedillo Tr. at 1415A-19A.

Doctors Ward and Griffin both had personal experiences with Dr. Wakefield that left them highly skeptical of his claims.

(1) Challenges to Dr. Wakefield's Research.

(a) Doctor MacDonald.

Doctor MacDonald criticized the 1998 Wakefield paper for its lack of proper controls, but focused much of his criticism on the misleading statements it contained. Doctor Wakefield reported that the children had food intolerance and abdominal pain. However, several of Dr. Wakefield's co-authors,[252] who were the physicians caring for the children, reported in a March 21, 1998, letter to *Lancet*, that the children suffered from severe constipation. Hazlehurst Tr. at 637A-38. The significance of this additional information is that lymphonodular hyperplasia is often caused by constipation. Hazlehurst Tr. at 628A. Doctor MacDonald characterized Dr. Wakefield's theory as "incredible," "fantastic," "improbable," and "not based on any data." Hazlehurst Tr. at 642A-43A.

Doctor MacDonald was even more critical of the Wakefield 2002 paper.[253] At the *Hazlehurst* hearing, he characterized the Wakefield 2002 paper as scientific deception. Hazlehurst Tr. at 646A-47A. He noted that the rates of inflammation documented in the pathology reports for the colon were similar for the autistic children and the control children. Although more of the autistic children had pathological findings in the ileum, Dr. MacDonald criticized the pathology reports for inventing new conditions and characterizing normal lymphoid follicles as pathologic abnormalities.

Doctor MacDonald also pointed out that the presence of LNH is neither evidence of inflammatory bowel disease nor inflammation.[254] Hazlehurst Tr. at 621A-23A. Doctor MacDonald testified that children generally have larger lymph nodes than adults do, particularly in the gastrointestinal tract, because they suffer from frequent gastrointestinal infections. A diagnosis of lymphonodular hyperplasia is a subjective diagnosis, based on the endoscopic examination. If the endoscopic examination reveals larger or more prominent lymph nodes, the examiner may diagnose lymphonodular hyperplasia. Since lymphoid follicles are part of the normal gastrointestinal tract, the condition cannot be diagnosed based on biopsy of the lymph

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[252] The letter was signed by Drs. Simon Murch, Mike Thompson, and John Walker Smith. Hazlehurst Tr. at 638.

[253] Doctor MacDonald's critique of this paper and of Dr. Wakefield's research was published. *See* T. MacDonald and P. Domizio, *Autistic enterocolitis; is it a histopathological entity?* HISTOPATHOLOGY 50: 371-79 (2007), filed as Hazlehurst Res. Ex. A, Tab 21.

[254] Doctor Krigsman, Michelle Cedillo's gastroenterologist, agreed that LNH is not necessarily a pathological process that needs to be treated, and might simply be the result of a transient illness, but noted that LNH is a response of the immune system to some stimulus. Cedillo Tr. at 550A-51A.

nodes, because the histology of the lymphoid follicles in LNH is identical to that of normal individuals. Hazlehurst Tr. at 616A-17B; Hazlehurst Res. Ex. H, at 978-979.[255]

Doctor MacDonald explained that it is normal to see a mild increase in inflammatory cells in the guts of children without IBD. However, because it would be unethical to subject children without gastrointestinal symptoms to colonoscopy and biopsy, it is difficult to determine the normal range of inflammatory cells in the gastrointestinal tract of children. Although such a study of normal children is prohibited by medical ethics, colonoscopies and biopsies of normal healthy adults without gastrointestinal symptoms found microscopic inflammation of the cecum.[256] Hazlehurst Tr. at 625A-27A.

During his testimony in *Hazlehurst*, Dr. MacDonald used four endoscopy photographs that appeared in Dr. Wakefield's 2002 paper as examples. Although the four photographs purportedly show ileum, Dr. MacDonald explained that the time stamps that appear on them indicated that Panel A was cecum, not ileum. He characterized this as "something of a deception." He also noted that the control children in this study did not have chronic constipation, which was the primary presenting symptom of the autistic children, and, thus, any comparison with the control children was misleading. Hazlehurst Tr. at 646A-49A.

(b) Doctor Rima.

With 15 years of experience in measles virology, Dr. Rima was very interested in Dr. Wakefield's first reports of an association of the MMR vaccine with gastrointestinal disease. He met Dr. Wakefield at a conference in 1992, where a number of measles virologists looked at the material Dr. Wakefield had produced. Doctor Rima attended two meetings, and concluded that the material produced in support of Dr. Wakefield's claims was highly selective, and that Dr. Wakefield was not responsive to criticisms of his findings. The cellular material that Dr. Wakefield claimed was measles virus was not measles virus. Snyder Tr. at 843A-46A.

In 1995, one of Dr. Wakefield's students approached Dr. Rima about co-authoring a paper. After examining the data supplied by the student, Dr. Rima concluded that the findings of measles virus were based on contamination from a measles virus clone he had previously supplied to Dr. Wakefield as a positive control for his research. When an abstract concerning positive results for the presence of measles virus was not retracted after Dr. Rima informed them of the contamination, Dr.

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[255] D. Levine and R. Haggitt, *Normal histology of the colon*, AM. J. SURG. PATHOL. 13 (11): 966-84 (1989).

[256] S. Paski, *et al., The Importance of Recognizing Increased Cecal Inflammation in Health and Avoiding the Misdiagnosis of Nonspecific Colitis*, AM. J. GASTROENTEROL. 102(10): 2294-99 (2007), filed as Hazlehurst Res. Ex. I.

Rima formally withdrew from his collaboration with Dr. Wakefield. Snyder Tr. at 844A.

(2) Investigations into Dr. Wakefield's Claims.

Doctor Fombonne was part of a panel convened by the U.K.'s Medical Research Council ["MRC"][257] to examine Dr. Wakefield's claims of measles virus causation of gastrointestinal illness. Cedillo Tr. at 2531-32. In 1998 or 1999, the MRC held hearings with Dr. Wakefield and experts in several fields. Doctor Rima, who was also familiar with the investigation, testified that the consensus was there was no substance to Dr. Wakefield's claim of measles vaccine or virus involvement in bowel syndromes. Snyder Tr. at 845A. Doctor MacDonald provided a great deal of information about the history of Dr. Wakefield's various claims of gut disorders being linked to the measles virus, and his evaluation of the evidence supporting those claims. Hazlehurst Tr. at 629A-49A.

According to Dr. MacDonald, the MRC investigation concluded that Dr. Wakefield was using reagents to identify measles virus that were not specific for that virus, and that important control measures were not being used. As a result, the Royal Free Hospital asked Dr. Wakefield to repeat the studies. No repeated study results have been published. Hazlehurst Tr. at 629A-632A.

Doctor Fombonne testified that he was part of the peer review process, and was charged with examining the epidemiological evidence to determine if it supported or refuted Dr. Wakefield's autistic enterocolitis hypothesis. Cedillo Tr. at 1239-40. He examined the incidence of IBD, including Crohn's disease, in two large groups of British children referred to a hospital where data on both psychiatric and medical conditions were collected. There were approximately 750 children with a diagnosis of PDD and about 8,000 control children with other psychiatric diagnoses. He also looked at epidemiologic data on French children, comparing a group of about 175 children with PDD diagnoses with over 5,000 children with other psychiatric diagnoses. Data on Crohn's disease and enterocolitis were available on all the children. Neither study demonstrated any increased incidence of IBD in children with PDD. Cedillo Tr. at 1425A-29A; Cedillo Res. Ex. P at 36-37.

(3) Conflicts of Interest.

Doctor Kinsbourne acknowledged that, at the time Dr. Wakefield published his1999 work on autistic enterocolitis, Dr. Wakefield had been asked by U.K. attorneys to become involved in the U.K. MMR litigation, and at the time of the Lancet publication, Dr. Wakefield had received funds from the attorneys involved in that litigation. Cedillo Tr. at 1198A-99A.

Doctor MacDonald noted that in 2005, Dr. Wakefield published yet another article involving the same children and the same information published earlier. He also

[257] The MRC is the U.K. equivalent of the NIH. Cedillo Tr. at 1246A.

pointed out that one of the co-authors on the paper, Kirsten Limb, was not a scientist, and was associated with the law firm representing the petitioners in the U.K. MMR litigation.[258] Hazlehurst Tr. at 657A-59. Doctor MacDonald also testified that Dr. Wakefield was undergoing a "fitness to practice" procedure in the U.K. Hazlehurst Tr. at 660.

Undisclosed in the articles co-authored by Dr. Wakefield, linking the MMR vaccine to gastrointestinal symptoms and autism, was any information concerning a patent application purportedly filed by Dr. Wakefield' for a monovalent measles vaccine. *See* Cedillo Res. Tr. Ex. 7. Doctor Kinsbourne testified that if Dr. Wakefield had such a patent and, thus, stood to gain financially from his criticisms of the MMR vaccine, his failure to disclose this in his research critical of the MMR vaccine would be "reprehensible." Cedillo Tr. at 1208. Cedillo Res. Tr. Ex. 7 was proffered as a copy of the patent application, with some supporting documentation. It is difficult to determine from an examination of the exhibit exactly what the patent application covered, whether it was for a monovalent measles vaccine or something else. It appears from the supporting documents that Dr. Wakefield was studying an "oral measles virus-specific dialysable lymphocyte extract transfer factor" (*id*. at 2). The remainder of the exhibit summarized findings from the 12 children featured in Dr. Wakefield's research. Respondent's counsel repeatedly referred to this exhibit as a patent application, without objection by petitioners. However, because the trial exhibit does not clearly indicate that it is a patent application filed specifically by Dr. Wakefield, in an abundance of caution, I have not considered this exhibit in reaching my findings in this case.

Also undisclosed in the 1998 LANCET publication was that at least some of the children studied were already claimants in the U.K. MMR litigation. Snyder Res. Ex O, Tab 11 (a statement by the editors of LANCET) at 820-21).

(4) Personal Experiences with Dr. Wakefield.

When Dr. Wakefield first began to implicate MMR as a cause of autism, he invited Dr. Griffin to the U.K. as a consultant, presumably based on her expertise with measles virology. Cedillo Tr. at 2832A. She spoke with people from his laboratory at an open scientific meeting where they indicated they were having problems getting their PCR testing to work. Cedillo Tr. at 2861A-62. It was quickly apparent to Dr. Griffin that Dr. Wakefield's laboratory personnel did not know how to perform PCR testing and analysis. Based on her personal interactions with Dr. Wakefield, she was suspicious of the research he did, and she declined the consultation offer. Cedillo Tr. at 2832A-33.

Doctor Ward testified that Dr. Wakefield presented data from an abstract of work done by Dr. Ward's laboratory as supportive of Dr. Wakefield's MMR-autism

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[258] A. Wakefield, *et al., The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder,* EUR. J. GASTROENTEROL. HEPATOL. 17: 827-36 (2005), filed as Cedillo Res. Ex. T, Tab 35.

hypothesis. Doctor Ward personally cautioned Dr. Wakefield against relying on this data because what was presented initially in the abstract turned out to be wrong.[259] Cedillo Tr. at 1864A-65.

2. The Revised Theory Advanced by Petitioners.

Petitioners' revised theory differs from Dr. Wakefield's in several respects. The revised theory relies upon the presence of primary and/or secondary immune system deficits, rather than solely upon the action of components of the MMR vaccine, to permit measles virus persistence in the gastrointestinal tracts and brains of children with regressive autism and gastrointestinal symptoms. Instead of opioid peptides traveling from the gut to the brain to cause autism, Dr. Kinsbourne's theory involved the measles virus itself traveling to the brain, and either causing inflammation, disrupting communication networks, or actually killing cells, causing over-excitation of the brain. Noting the co-occurrence of gut problems and regressive autism,[260] Dr. Kinsbourne argued that Occam's razor[261] favored an explanation that could account for both the CNS and gut symptoms in children with autistic enterocolitis. Cedillo Pet. Ex. 61 at 12-14. According to Dr. Kinsbourne, a persistent measles virus infection could account for both an encephalopathy and gut disorders. *Id*., at 13-14.

a. Gut Disorders and Autism.

Although the lynchpin of petitioners' case is the Unigenetics' laboratory test results that found measles virus in gut tissue, CSF, and peripheral blood of children with autism, petitioners introduced other evidence purporting to show the existence of autistic enterocolitis. Unigenetics' testing program is addressed in Section VII, below. The testimony about the postulated link between gut disorders and regressive autism on the general causation issue was provided primarily by Dr. Krigsman.

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[259] What appears to be Dr. Wakefield's account of this meeting appears in Snyder Pet. Ex. 27 at 10. Doctor Wakefield characterizes Dr. Ward as being annoyed, but says nothing about Dr. Ward telling him that the abstract was based on errors. Doctor Wakefield implied that Dr. Ward was withholding data that would have confirmed Dr. Wakefield's findings. I accept Dr. Ward's account as correct.

[260] It seems clear that children with autism experience more gastrointestinal symptoms, with slightly greater frequency, than do other children. *See* Vallicenti-McDermott, Cedillo Pet. Ex. 61, Tab HHHH. This cross-sectional study compared lifetime prevalence of gastrointestinal symptoms in children with ASD, children with typical development, and children with other developmental disabilities. A history of gastrointestinal symptoms was elicited in 70% of children with ASD, compared with 28% of children with typical development and 42% of those with other developmental disabilities. The incidence of an abnormal stool pattern was higher in children with ASD (18%) than in those with typical development (4%) and those with other developmental disabilities (2%). Two shortcomings exist in this study: it is based on parental reports, rather than medical records, and it does not distinguish between classic and regressive autism. Children with ASD are more likely to have pica or self-restricted diets. Cedillo Tr. at 2716A-17A.

[261] Doctor Ward's report also referenced Occam's Razor, explaining that it meant "assumptions to explain anything should not be multiplied beyond necessity." Snyder Res. Ex. K. at 5.

In Dr. Krigsman's general pediatric practice, he noted a higher incidence of gut disorders in children with autism. In 2001, he read an article describing a group of autistic children with histories involving chronic diarrhea and chronic abdominal pain, which were identical to the symptoms he observed in his practice. Cedillo Tr. at 415-17. The article was published in September 2000 in the American Journal of Gastroenterology.[262] The authors performed diagnostic colonoscopies on a group of these children, determining that they had a nonspecific inflammation of the colon and the end of the ileum. Cedillo Tr. at 416A.

Thereafter, Dr. Krigsman contacted the patients that had been referred to him and performed diagnostic colonoscopies, finding the same nonspecific colitis found in Dr. Wakefield's study.[263] Cedillo Tr. at 417-18. His endoscopic examinations showed varying combinations of redness, ulcerations, and cryptitis. The pathology reports in the majority of the children showed chronic and/or active colitis. Some patients showed a crypt abscess, demonstrating more advanced inflammation. Cedillo Tr. at 420-21. Based on these findings, Dr. Krigsman drew a connection between their autism diagnoses and their bowel symptoms. Cedillo Tr. at 419.

Doctor Krigsman began treating the children who had enterocolitis with oral anti-inflammatory drugs, the same drugs commonly used to treat IBD, often seeing marked improvement in the pain and diarrhea. He testified that their response to this treatment indicated that they were suffering from intestinal inflammation, but it did not prove that they had IBD. Cedillo Tr. at 422-23.

Doctor Krigsman also testified about his own research into the cause of autistic enterocolitis. This research had not been published, but his preliminary data appeared in an abstract and a poster presentation at the International Meeting For Autism Research ["IMFAR"]. The poster described finding vaccine strain measles virus RNA in lymphonodular tissue that Dr. Krigsman collected during endoscopies of autistic children with gastrointestinal symptoms. The abstract was filed as Cedillo Pet. Ex. 59, Tab K, and a photocopy of the poster was filed as Cedillo Pet. Tr. Ex. 3. His research project attempted to confirm Dr. Wakefield's findings of measles virus in inflamed intestinal tissue. Cedillo Tr. at 480. Doctor Krigsman indicated that 35 specimens tested positive for measles virus, with six of those specimens testing positive for

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[262] Although Dr. Krigsman did not identify the article, and identified the author as Dr. John Walker Smith (Cedillo Tr. at 415-16A), it appears that he was referring to another of Dr. Wakefield's publications. *See* A. Wakefield, *et al.*, *Enterocolitis in Children with Developmental Disorders,* AM. J. GASTROENTEROLOGY 95(9): 2285-95 (2000), filed as Cedillo Pet. Ex. 61, Tab NNN. Doctor Walker Smith was a co-author of this article.

[263] During cross-examination, Dr. Krigsman testified that Lenox Hill hospital's management believed he was performing unnecessary endoscopies on autistic children. Whether these particular procedures were the basis of the hospital's concern was unclear from the testimony. Cedillo Tr. at 499A-500.

vaccine strain measles virus RNA.[264] Cedillo Tr. at 487A-88A. Based on these results, he was confident that measles virus was responsible for the bowel inflammation in his autistic patients. In drawing this conclusion, he relied on the work performed at Unigenetics, which found measles virus in gut tissue. Cedillo Tr. at 488A-90. He deferred discussion of the methodology of the PCR testing performed, indicating that Drs. Hepner and Kennedy would discuss those results. Cedillo Tr. at 487A. Further discussion of the IMFAR presentation is contained in Section VII, below.

In his expert report, Dr. Krigsman described autistic enterocolitis as a "constellation of gastrointestinal *symptoms* including diarrhea, (vomiting) [sic], abdominal pain, difficulty in passing stool diarrheal stool [sic], and abdominal distention." Cedillo Pet. Ex. 59, at 7 (emphasis original). However, this description is of irritable bowel syndrome, not inflammatory bowel disease. He stated that children with autism, and primarily those with regressive autism, have esophagitis, gastritis, and enterocolitis. *Id.*

He testified that children with developmental disorders who fail to have one formed stool per day merit medical attention and a thorough history, and may warrant diagnostic endoscopy and colonoscopy. Children with autism who do not have gastrointestinal symptoms may have silent disease, masked by their inability to indicate pain. Cedillo Tr. at 496-498A. He testified that marked LNH occurs in colitis, Crohn's disease, and gastritis, but that in an otherwise healthy patient, LNH would not be indicative of a problem. However, in his experience with over 100 patients, those with LNH were more likely to have inflammatory processes than those without it. He had not published these results. Cedillo Tr. at 550A-51A.

Doctor Hanauer, respondent's gastroenterology expert, took issue with a number of Dr. Krigsman's statements. Although much of his testimony was focused on Michelle Cedillo's diagnosis and treatment, he also clarified the distinctions between IBS and IBD which were somewhat conflated in Dr. Krigsman's testimony and his expert report. *See* Cedillo Tr. at 2088-92A, 2107-08A. Doctor Hanauer was quite clear that Dr. Krigsman's view that autistic enterocolitis was a new bowel disorder was not recognized by the gastroenterology medical community or medical textbooks. Cedillo Tr. at 2143; Cedillo Res. Ex. T at 16.

The autistic enterocolitis theory was obliquely supported by an article filed as Cedillo Pet. Ex. 61, Tab B.[265] Doctor Paul Ashwood reported on tissue biopsies from autistic children with gastrointestinal symptoms that were compared to samples from

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[264] The remaining 29 specimens had been sequenced, but not yet tested to determine if the virus was vaccine strain. Cedillo Tr. at 487A-88A.

[265] P. Ashwood, *et al., Spontaneous Mucosal Lymphocyte Cytokine Profiles in Children with Autism and Gastrointestinal Symptoms: Mucosal Immune Activation and Reduced Counter Regulatory Interleukin-10,* J. CLIN. IMM. 24(6): 664-73 (2004), filed as Cedillo Pet. Ex. 61, Tab B ["Ashwood 2004"]. Doctor Wakefield was a co-author of this article.

typically developing children, only some of whom had gastrointestinal problems. Histological testing showed that the tissues from the autistic children had much higher levels of pro-inflammatory cytokines, and much lower levels of regulatory cytokines, than the control group. The authors opined that this imbalance supported a hypothesis of mucosal immunopathology in the gastrointestinal tracts of autistic children afflicted with intestinal symptoms. The authors recommended various dietary changes to treat the inflammation. Doctor Krigsman cited this article for the proposition that the clinical picture of IBD "is, in its entirety, identical with the clinical picture seen in other children with autistic enterocolitis in whom measles virus has been identified in the bowel." Cedillo Pet. Ex. 59 at 6. Doctor Kinsbourne asserted that the article demonstrated that ILNH is "a disease of the gut that is predominantly found in children with autistic spectrum disorder [which] has been repeatedly demonstrated." Cedillo Pet. Ex. 61 at 13.

Doctor MacDonald was highly critical of Dr. Ashwood's findings and sampling techniques. He noted that in an earlier work by Ashwood,[266] the biopsy samples in the autistic children and the control children were not taken from the same types of tissue. With regard to Ashwood's 2004 paper, Doctor MacDonald indicated that he peer reviewed another version of it for a different scientific journal, and commented in that review that the cell yields claimed could not be correct. The article claimed that the cytokine levels in autistic children were the same as those found in children with Crohn's disease, a claim that Dr. MacDonald characterized as "not biologically plausible," considering the severe inflammation in Crohn's patients versus the mild inflammation observed in the autistic children. Hazlehurst Tr. at 654A-56B. Biomarkers of inflammation in autistic children indicate that they do not have inflammation in their gastrointestinal tracts. Hazlehurst Tr. at 627A.

Epidemiologic evidence indicates that children with regressive autism do not have higher rates of IBD than autistic children without regression. Cedillo Tr. at 1425-29A. The children with regression had more bowel symptoms, however.[267] A 2002 time-trend study by Taylor[268] examined the rate of bowel problems lasting three months or longer in children with regression, during periods both before and after the introduction of the MMR vaccine. The study found no significant difference in the rates of bowel problems or regression over a 20-year period. The authors noted a possible

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[266] P. Ashwood, *et al., Intestinal Lymphocyte Populations in Children with Regressive Autism: Evidence for Extensive Mucosal Immunopathology*, J. CLIN. IMMUNOL. 23(6): 504-17 (2003), filed as Cedillo Pet. Ex. 63, Tab D ["Ashwood 2003"].

[267] Richler, filed as Cedillo Res. Ex. DD, Tab 12. A diagnosis of IBD requires a finding of inflammation in the digestive tract; bowel symptoms could include diarrhea, constipation, or abdominal pain. Cedillo Tr. at 2088A-90A.

[268] B. Taylor, *et al., Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study*, BRITISH MED. J. 324: 393-96 (2002) ["Taylor 2002"], filed as Cedillo Res. Ex. P, Tab 146.

association between nonspecific bowel problems and developmental regression, but the association was not related to MMR vaccination status. Cedillo Res. Ex. P, Tab 146, at 394; Cedillo Tr. at 2564A-66A.

Doctor Zimmerman indicated that about 24% of autistic children have gastrointestinal symptoms, most of which improve as the children grow older. Cedillo Res. Ex. FF at 2. Doctor Fombonne's estimates were slightly lower, with about 10-20% of the autistic children he sees having temporary bowel symptoms. Some had symptoms of longer duration. He believed that many of the gastrointestinal problems are caused by poor diet or pica. Cedillo Tr. at 2716A-17A. Typically developing children also display gastrointestinal symptoms, with one cohort study finding between 11-24% of children under five years of age having three or more medical visits for abdominal pain and constipation.[269]

I found the evidence supporting the regressive autistic enterocolitis phenotype to be scanty, and Dr. Krigsman's problems with medical authority and his own "resume padding" did not enhance his credibility. There was substantial evidence that contradicted the theory, provided in the form of testimony and reports from well-qualified witnesses (Drs. Hanauer and MacDonald), the expert report of Dr. Gershon, and a substantial number of journal articles. Many autistic children do appear to have co-occurring gastrointestinal symptoms, but this is without regard to whether they also experienced regression. They do not appear to experience higher levels of inflammatory bowel disease. The evidence for ILNH as a new disease related to regressive autism is not sufficient to demonstrate a separate phenotype of regressive autistic enterocolitis.

b. The Causation Theories.

(1) Doctor Kinsbourne's Theories.

Doctor Kinsbourne played the central role for petitioners in the Theory 1 test cases. He "connected the dots" in the general causation case among Dr. Byers' opinions on immunology and immune functioning in ASD, Dr. Kennedy's opinions on virology and measles virus persistence, Dr. Krigsman's opinions on gastroenterology and gut disorders in ASD, and Dr. Aposhian's opinions on mercury toxicology and the role of TCVs in ASD. All of these experts' opinions, with the exception of Dr. Aposhian's, rested on the actual presence of measles virus in children with ASD. Doctor Kinsbourne's role was to provide the theory or theories to explain how measles virus could, directly or indirectly, cause at least some cases of ASD.

He initially offered two somewhat related theories to explain how measles virus

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[269] *See* D. Chitkara, *et al.*, *Incidence of Presentation of Common Functional Gastrointestinal Disorders in Children from Birth to 5 Years: A Cohort Study*, CLIN. GASTROENT. HEPATOL. 5: 186-91 (2007), filed as Cedillo Res. Ex. T, Tab 5.

could cause regressive autism. The first theory was that the virus caused an inflammatory process in the brain leading to an encephalopathy. The second theory, built in some measure on the first, relied on persistent measles virus causing inflammatory damage to cells, leading to an imbalance in the excitation-inhibition chemicals in the brain. This imbalance manifested in the behavioral and communication disorders that are autism's core features. Between the *Cedillo* hearing in June, 2007, and the filing of post-hearing briefs in *Snyder* in March, 2008, Dr. Kinsbourne reformulated the theories linking the neuroinflammation theory more closely with the over-arousal theory.[270] In his supplemental report,[271] he referred to his theory's three points as causally linked "stages," set forth below:

Stage 1. Neuroinflammation was caused by activation of the brain's innate immune system, mediated by microglial activation. Activated microglia released cytokines, causing damage to astrocytes. The damaged astrocytes could not mop up the excess glutamate and brain glutamate levels rose.

Stage 2. Excess glutamate led to: (a) over-activation and/or over-arousal of the brain; (b) which could cause seizure activity; and (c) neuronal death as the result of excitotoxicity.

Stage 3. Neural activation and over-arousal could account for autistic behavior. Snyder Pet. Ex. 215 at 1.

(a) Stage 1.

Doctor Kinsbourne theorized that measles virus from the gut entered the CNS by breaches in the blood-brain barrier caused by the release of proinflammatory cytokines.[272] Once in the brain, the virus could affect several types of brain cells,

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[270] After the conclusion of the causation hearing in *Snyder*, petitioners requested the opportunity to file a supplemental expert report by Dr. Kinsbourne. *See* Motion for Leave to File Supplemental Report of Dr. Marcel Kinsbourne Contemporaneous with Petitioners' Post-Hearing Brief, dated February 7, 2008. I granted their request, over respondent's objections, giving respondent the opportunity to file a supplemental expert report in response. *See* Order, dated February 28, 2008. Petitioners filed Dr. Kinsbourne's supplemental report on March 10, 2008, as Snyder Pet. Ex. 215. Respondent filed the supplemental response of Dr. Wiznitzer on April 10, 2008, as Snyder Res. Ex. DD.

[271] Accompanying Dr. Kinsbourne's report were eighteen additional references, only one of which could not have been furnished with his original report. Most of Dr. Kinsbourne's supplemental report consisted of sur-rebuttal to points made by Dr. Wiznitzer during his testimony at the *Snyder* hearing. As respondent noted in his opposition to the supplemental report, given Dr. Kinsbourne's presence throughout the *Snyder* hearing, he was available for recall to answer Dr. Wiznitzer's criticisms at the time of the hearing. Nevertheless, I considered both Drs. Kinsbourne's and Wiznitzer's supplemental reports.

[272] Doctor Byers testified that one specific cytokine, TNF-α, causes the blood-brain barrier to become more permeable, increasing the ability of cytokines to reach brain tissues. Cedillo Tr. at 919.

specifically, neurons or glia.[273] Cedillo Tr. at 1082, 1086.

To establish the presence of measles virus in the brain, Dr. Kinsbourne relied upon the findings of measles virus in the CSF (in Colten's case), or in the gut (in Michelle Cedillo's case), based on the results of testing by Unigenetics. Unigenetics' testing is addressed in Part G, below.

To establish brain inflammation in those with ASD, he relied upon a paper by Vargas,[274] co-authored by one of respondent's experts, Dr. Zimmerman, that found an inflammatory process involving glial activation in the brains of autistic children. Snyder Tr. at 464A-65A. According to Dr. Kinsbourne, the presence of inflammation indicated an ongoing, long-term disease process, rather than a static process caused by prenatal damage to the brain. In his view, the type of inflammation found, activated microglia, indicated an innate immune system response to the presence of an agent recognized as foreign.[275] Snyder Tr. at 465A-67A.

He theorized that, once activated by a foreign antigen, microglia release cytokines, causing either localized or systemic inflammation. Cedillo Tr. at 1084A; Snyder Tr. at 467A-68A. The source of the foreign antigen (such as a virus) could be inside brain cells, stimulating an immune response inadequate to kill the pathogen, but capable of damaging innocent bystander cells, such as astrocytes (astroglia). He noted that studies had found microglial activation in the brains of individuals with ASD. Activated microglia release proinflammatory cytokines. Activated astrocytes release glutamate as a result of proinflammatory cytokines. Cedillo Tr. at 1091-92A; Snyder Tr. at 467A-68A.

Doctor Kinsbourne's report also indicated that chronic inflammation had been found in the cerebrum and the cerebellum of children with ASD. He considered this finding consistent with the effects of a chronic viral infection. Cedillo Pet. Ex. 61, at 17-

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[273] There are two main categories of brain cells: neurons and glia. Neurons perform brain functions and control other body systems. Glia act like the connective tissue found in other organs and also function as immune cells in the brain. Astroglia (astrocytes), a specialized form of glia shaped like stars, are very prevalent in the brain and are scattered among the neurons. Microglia are the brain's innate immune system. Oligodendroglia are the cells that manufacture the fatty sheaths along axons, called myelin. Myelin acts as insulation along the axons, similar to the role of plastic coating along electrical wires. Cedillo Tr. at 1074-75A.

[274] D. Vargas, *et al., Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism,* ANNALS NEUROL. 57(1): 67-81 (2005) ["Vargas 2005"], filed as Cedillo Pet. Ex. 61, Tab MMM.

[275] Doctor Kinsbourne agreed that microglial activation might have other causes, including activation in response to a breakdown of neurons. Microglial activation is found in both Parkinson's disease and Alzheimer's. Cedillo Tr. at 1091. The Vargas 2005 article cited by Dr. Kinsbourne indicated that the inflammatory processes observed in autistic brains resemble those seen in Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, and have some similarities to those seen in HIV infection. They did not find adaptive immune reactions in the ASD patients. The authors noted that co-morbid conditions, such as epilepsy, might play a role in their findings.

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Doctor Wiznitzer disagreed with Dr. Kinsbourne's assertion that the Vargas paper supported his theory. Doctor Wiznitzer noted that the authors did not suggest that the inflammation found was the result of a chronic infection, any type of measles infection, or excess glutamate production. They did not advocate that the innate inflammatory responses observed were the cause, rather than the effect, of the brain pathology commonly found during autopsies of individuals with ASD. Cedillo Tr. at 1783A-84A. *See also* C. Pardo, *et al., Immunity, neuroglia and neuroinflammation in autism*, INT'L REV. PSYCHIATRY 17(6): 485-95 (2005), filed as Cedillo Pet. Ex. 61, Tab ZZZ (question of whether neuroinflammation found was a cause or an effect was not resolved).[276]

Doctor Ward noted that children may have brain inflammation for prolonged periods without a cause being identified. However, that prolonged inflammation does not lead to the development of ASD, with the very limited exception of herpes encephalitis, which causes autistic-like behaviors. The brain lesions found in victims of herpes encephalitis do not resemble those observed in the brains of ASD patients. Cedillo Tr. at 1813A-15. In herpes encephalitis, it is this brain damage, not a lingering viral influence, that is responsible for the autistic-like behavior of the children. Snyder Tr. at 726A-27A. Doctor Wiznitzer concurred, noting that children who have congenital herpes simplex encephalitis have developmental problems that are best described as "autistic-like," in that they manifest behaviors that are on the autism spectrum, but their behavior is different from most ASD patients Dr. Wiznitzer has seen. Snyder Tr. at 724A-25A.

Doctor Kinsbourne addressed other neuropathology findings in the brains of ASD patients by noting that autopsies had found a "shortage" of pyramidal cells in the cerebellar cortex without evidence of necrosis (dying neurons). Snyder Tr. at 462A. Based on the findings of inflammation in the brain, his "working model" was that the innate immune system, in an effort to kill an invading pathogen such as the measles virus, damaged astrocytes or other cells in the vicinity of the infected cells. He attributed the small amount of gliosis found during autopsy to the death of astrocytes and other glial cells. Snyder Tr. at 462A-68A.

Doctor Wiznitzer also challenged Dr. Kinsbourne's statement that the cerebral and cerebellar changes in the brains of children with ASD were consistent with the effects of a chronic viral infection, noting that there was no support for this statement in the medical literature. Cedillo Tr. at 1740A-41A. In support of his testimony, Dr.

[276] Doctors Vargas and Zimmerman were co-authors of this article.

Wiznitzer cited several articles by Drs. Bauman and Kemper.[277] Their pathology studies of the brains of individuals with ASD consistently showed significant abnormalities in the limbic system, cerebellum, and related inferior olive, including small cell size and increased cell packing density. The most consistent finding was a reduced number of Purkinje cells. Although Bauman and Kemper indicated that the neurobiological processes involved in autism might involve postnatal factors, the authors did not suggest that the postnatal factors included inflammation or infection. Bauman and Kemper 2005, Cedillo Pet. Ex. 61, Tab I.

As support for Stage 1 of his theory, Dr. Kinsbourne's supplemental report cited an article by Bezzi,[278] which indicated that activated microglia can amplify glutamate release from astrocytes. *See* Bezzi, Snyder Pet. Ex. 103 at 706. In his supplemental report, Dr. Wiznitzer acknowledged that this paper supports the proposition that activated microglia amplify glutamate release, but noted that, in this study, the excess glutamate caused neuronal death. Snyder Res. Ex. DD at 1-2.

Doctor Kinsbourne also cited the only newly-published journal article he filed with his supplemental report, Snyder Pet. Ex. 233,[279] in support of Stage 1 of his theory. This article, co-authored by Dr. Martha Herbert, is similar to her earlier article, filed as Cedillo Pet. Ex. 61, Tab FF,[280] which Dr. Kinsbourne mentioned frequently in his testimony in *Cedillo*. Like her earlier article, it is a thoughtful and extensively researched publication that combines a literature survey with a number of hypotheses and suggestions for future research. It is clearly not offering evidence for a causal theory; the article discussed innate immune inflammation with the caveat: "However, we must point out that this is simply an alternative view point...". Anderson, Snyder Pet. Ex. 233 at 171. Doctor Kinsbourne correctly asserted that the article's abstract discussed possible effects of innate immune inflammation on neurosignaling.

However, the Anderson article, read in context, does not support Stage 2 of his revised and combined theory of excessive glutamate production. The specific sections of the article dealing with innate immune inflammation did not discuss glutamate imbalance as an effect of such inflammation. Instead, the authors referred to the effects of HIV encephalopathy, and noted that evidence of inflammation found in the

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[277] The most recent of these articles filed is M. Bauman and T. Kemper, *Neuroanatomic observations of the brain in autism: a review and future directions*, INT'L. J. DEV. NEUROSCIENCE 23: 183-87 (2005) ["Bauman and Kemper 2005"], filed as Cedillo Pet. Ex. 61, Tab I.

[278] P. Bezzi, *et al.*, *CXCR4-activated astrocyte glutamate release via TNFα: amplification by microglia triggers neurotoxicity*, NAT. NEUROSCI. 4(7): 702-10 (2001), filed as Snyder Pet. Ex. 103 ["Bezzi"].

[279] M. Anderson, *et al.*, *Bridging from Cells to Cognition in Autism Pathophysiology: Biological Pathways to Defective Brain Function and Plasticity*, AM. J. BIOCHEM. BIOTECH. 4(2): 167-76 (2008) ["Anderson"].

[280] M. Herbert, *Autism: A Brain Disorder or a Disorder that Affects the Brain?* CLIN. NEUROPSYCHIATRY 2(6): 354-79 (2005).

dendritic beading observed in HIV dementia has not been shown to exist in autism. It also discussed innate immune inflammation's effects in disrupting the synchronized firing of neurons. Anderson, Snyder Pet. Ex. 233 at 171.

(b) Stage 2.

Building on a theory he advanced in 1980 in one of his few publications on autism,[281] Dr. Kinsbourne explained that many of the symptoms of autism can be explained by "an over-activation of arousal symptoms in the autistic person." In his opinion, many of the stereotyped or repetitive movements made by autistic children have a calming effect and are performed when the child become overaroused or overexcited. Cedillo Tr. at 1096-97. The over-arousal is, in his opinion, caused by a glutamate-gamma aminobutyric acid ["GABA"] imbalance in the brain, triggered by the death or incapacitation of astrocytes.

Doctors Wiznitzer and Dr. Kinsbourne agreed that glutamate is the predominant excitatory neurotransmitter in the brain, and that GABA is the predominant inhibitory neurotransmitter. The balance between these two neurotransmitters is the main factor in determining the level of brain excitation or inhibition. Excess glutamate is harmful. Snyder Pet. Ex. 29 at 18; Snyder Tr. at 691A-93. GABA, which is manufactured by cells from glutamate, is dependent on astrocytes. Snyder Tr. at 702A. Both experts agreed that one function of astrocytes is to regulate the level of glutamate at the synapse, recycling excess glutamate through the glutamate transporter system expressed on the astrocytes. Snyder Pet. Ex. 29 at 18-19; Snyder Tr. at 700-01A. This was the extent of their agreement.

In support of his theory, Dr. Kinsbourne cited a paper by Rubenstein and Merzenich, filed as Cedillo Pet. Ex. 61, Tab CCCC.[282] This article discusses the theory that some forms of autism are the result of "a disproportionate high level of excitation (or disproportionately weak inhibition) in neural circuits." *Id*. at 256. The authors advanced several possible causal mechanisms of overexcitation, including the presence of too many glutamate receptors, receptors that are too sensitive to glutamate's effects, too many neurons producing glutamate, or another mechanism by which a neuronal signal is inordinately amplified. The article also discussed the possibility that some forms of autism might be attributed to decreased inhibition, caused by deficient production of GABA, poor GABA signaling, too few neurons producing GABA, or deficiencies in GABA receptors.

In discussing Stage 2(a) of his theory, Dr. Kinsbourne's supplemental report

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[281] M. Kinsbourne, *Do Repetitive Movement Patterns in Children and Animals serve a Dearousing Function?* J. DEV. BEHAVIORAL PEDIATRICS 1(1): 112-17 (1980), filed as Cedillo Pet. Ex. 61, Tab OO.

[282] J. Rubenstein and M. Merzenich, *Model of autism: increased ratio of excitation/inhibition in key neural systems*, GENES, BRAIN AND BEHAVIOR 2: 255-67 (2003).

indicated that he was postulating a glutamate excess sufficient to cause over-arousal, but insufficient to cause excitotoxicity, at least in the initial stages of autism. Snyder Pet. Ex. 215 at 3. Astrocytic regulation of glutamate at the synapses ordinarily keeps excess glutamate from building up there and spreading to other synapses. Snyder Tr. at 701A. Doctor Kinsbourne's position was that an excess level of glutamate might be insufficient to kill many cells, but it could be sufficient to cause overexcitation, with predictable effects on brain function. Snyder Pet. Ex. 29 at 18-19. The glutamate excess could also be caused by malfunctioning or dying astrocytes. *Id.* at 19. Doctor Wiznitzer described Dr. Kinsbourne's statements that malfunctioning or dying astrocytes would suppress GABA inhibition as too simplistic to reflect accurately what would happen *in vivo*. Snyder Tr. at 702A-04. Doctor Wiznitzer explained that an excitatory-inhibitory process is always ongoing in the brain. Snyder Tr. at 706. Overexcitation of the brain can present with subjective symptoms and physical manifestations (neurological signs). Snyder Tr. at 706. When GABA levels are abnormal, seizures result. Snyder Tr. at 707.

In Stage 2(b) of Dr. Kinsbourne's theory, the elevated glutamate levels eventually rise to the point that epilepsy ensues, at least in some individuals. In support, Dr. Kinsbourne noted that many autistic children develop seizures and many have subclinical disturbances on EEG without frank seizures. He asserted that an article by Lewine[283] supported findings of epileptiform activity during sleep in children with regressive autism. The authors of this study compared brain electrophysiology in children with Landau-Kleffner syndrome[284] with children who had regressive ASD. Eighty-two percent of the children with ASD displayed epileptiform activity using the more sensitive MEG imaging system. Lewine, Snyder Pet. Ex. 225 at 406-07. The epileptiform activity observed in the ASD children was similar to, but more extensive than, that of the LKS children. There were no controls, either of typically developing children or those with early onset ASD. The authors did note that their preliminary work

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[283] J. Lewine, *et al., Magnetoencephalographic ["MEG"] Patterns of Epileptiform Activity in Children with Regressive Autism Spectrum Disorders*, PEDIATRICS 104(3): 405-18 (1999), filed as Snyder Pet. Ex. 225 ["Lewine"]. The MEG imaging system permits the location of the electrical discharges to be determined with greater precision than the traditional EEG.

[284] Children with this syndrome ["LKS"] experience an acquired language disorder, most probably as a result of a form of epilepsy. Lewine, Snyder Pet. Ex. 225 at 405. *See also* Cedillo Res. Ex. DD at 2 and P. Pearl, *et al.*, *The Landau-Kleffner Syndrome*, EPILEPSY CURR. 1: 39-45 (2001), filed as Cedillo Res. Ex. DD, Tab 9. Landau-Kleffner syndrome involves paroxysmal EEG discharges (sleep-activated), predominating over the temporal or parieto-occipital regions, and language deterioration (acquired aphasia), with manifestation at three to nine years of age. Word deafness is the first manifestation, with parents reporting that children no longer respond to commands. This may deteriorate into total unresponsiveness or impaired expressive communication. This language disorder has similarities to ASD, including abnormal development of spoken language, impaired ability to initiate or sustain conversation, and stereotyped, repetitive, and idiosyncratic language. Differences between the two syndromes include an earlier loss of language in ASD, more dramatic loss in LKS, and a different behavioral profile in ASD (core symptoms of ASD). EEG findings in LKS are striking. The etiology of LKS is unknown. Corticosteroid treatment in LKS has proven effective for both clinical and EEG abnormalities, suggesting a chronic encephalitic etiology. Lewine, Snyder Pet. Ex. 225 at 416-17.

on children without regression showed 70% of children with early onset ASD had similar epileptiform activity. Lewine, Snyder Pet. Ex. 225 at 413. Doctor Wiznitzer pointed out that the studied population discussed in the Lewine paper was a highly selected group and, thus, no conclusions could be drawn about the frequency of epileptiform activity in the ASD population as a whole. Cedillo Res. Ex. DD at 2.

Excess glutamate will render the brain more prone to epileptic discharges (Snyder Tr. at 698; Snyder Pet. Ex. 29 at 18-19) and Dr. Kinsbourne implied that the epilepsy and subclinical EEG disturbances that are common in ASD were the result of glutamate imbalance. Doctor Wiznitzer pointed out that if they were the result of a glutamate imbalance, with excess glutamate responsible for both the ASD and the seizures, the seizures would begin at the same time as the symptoms of ASD. However, epilepsy in autism classically begins at adolescence and young adulthood. Snyder Tr. at 698-99A. He did not believe that the glutamate-GABA balance could be slightly skewed, causing ASD, and then swing further out of balance to cause apoptosis, with resulting seizures. Snyder Tr. at 697A. Additionally, he noted that those with ASD who are most prone to develop seizures are those with the lower degrees of mental functioning. The lower the IQ, the more likely seizures are to occur. In those with ASD and normal intelligence, the risk of seizures is only slightly higher than that of the general population. Doctor Kinsbourne's theory did not explain why the glutamate imbalance he postulated would swing more wildly in children with lower degrees of mental functioning. Snyder Tr. at 699A-700. Doctor Wiznitzer also noted that the subclinical EEG disturbances in some children with ASD are not epileptic discharges. Snyder Tr. at 700.

Stage 2(c) of Dr. Kinsbourne's revised theory attributed the Purkinje cell loss to excitotoxic cell death sufficient to cause the loss of these cells, but presumably not sufficient to kill other neurons. Snyder Pet. Ex. 29 at 18-19. He cited articles by several authors in support, including Palmen,[285] Harding and Copp,[286] Hamann,[287] and

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[285] S. Palmen, *Neuropathological findings in autism,* BRAIN 127(12): 2572-83 (2004), filed as Snyder Pet. Ex. 229 ["Palmen"]. This article is a literature survey.

[286] This article was not filed as an exhibit. Doctor Kinsbourne's references to it were drawn from summarizations and quotations found in the Palmen article, *supra,* n. 285. He also quoted from an article by Kern published in 2003, which was not filed, but which was summarized and quoted in the Palmen article. Doctor Kinsbourne did not mention a 2002 article by Welsh, but it was the source of one of his quotations, not the Kern article he cited.

[287] M. Hamann, *et al.,The electrical response of cerebellar Purkinje neurons to simulated ischaemia,* BRAIN 128: 2408-20 (2005), filed as Snyder Pet. Ex. 223. This study examined the effect of ischemic insults on Purkinje and pyramidal cells, finding that excess glutamate led to Purkinje cell death. However, the study also found that glial glutamate transporters did not play a role in the excess glutamate released by ischemic insult. *Id.* at 2418.

Monnerie.[288] He suggested that, in late onset (regressive) ASD, the loss of Purkinje cells in the cerebellum could be due to excitotoxicity (Snyder Pet. Ex. 215 at 4), noting that the vulnerability of Purkinje cells to excitotoxicity was well known. In support, he referenced two journal articles cited by Palmen, neither of which was filed in this case. Snyder Pet. Ex. 215 at 5. Not having the opportunity to see the entirety of what those authors said, and the research context in which the references were made, I find that these citations add little to Dr. Kinsbourne's opinion. The Palmen article also noted that "[a]s to the timing of the neuropathological abnormalities in autism, all authors have suggested a prenatal origin, most probably during the first 6 months of gestation." Palmen, Snyder Pet. Ex. 229 at 2580. Read in their entirety, the cited articles provide no concrete support for Dr. Kinsbourne's theories.

The filed articles concerning Purkinje cells and their vulnerability to glutamate concentrations were all *in vivo* studies, with carefully controlled glutamate excesses. None of them provided substantial support for Dr. Kinsbourne's statement that: "[t]here is reason to suppose that in some cases Purkinje cells are depleted in the cerebellum of individuals with autism because of postnatal neuronal cell death." Snyder Pet. Ex. 215 at 5. Doctor Kinsbourne also suggested that the loss of synaptic connections and diminished dendritic growth in connection with the pyramidal cells in the hippocampus was the result of the cytotoxic effect of excess glutamate. Snyder Pet. Ex. 29 at 18-19.

Doctor Wiznitzer disagreed with Dr. Kinsbourne that a glutamate excess would kill Purkinje cells while sparing other neurons, although he agreed with Dr. Kinsbourne that excess glutamate was cytotoxic. He was not aware of any evidence that a glutamate excess could harm certain neuron types, while sparing others. Snyder Tr. at 693-94A. He also disagreed that loss of synaptic connections and diminished dendritic growth could be the result of excess glutamate, noting that such a glutamate excess would likely kill the cell outright. Snyder Tr. at 696. He questioned Dr. Kinsbourne's use of the Monnerie article as support for the loss of synaptic connections and diminished dendritic growth without neuronal cell death. He observed that Monnerie's experiments were performed on embryonic mouse neurons, a type of cell resistant to the amount of glutamate involved, with a short term exposure (days, rather than years). Snyder Res. Ex. DD at 3. Doctor Wiznitzer also noted the type of loss described from glutamate excess was dendritic injury (beading and spine loss), not consistent with the pathological findings in autopsies of ASD patients.

The most basic disagreement between the two pediatric neurologists about Stage 2 of Dr. Kinsbourne's theory was whether a glutamate-GABA imbalance could be sufficiently skewed so as to cause neurologic effects (over-arousal and seizure activity), but insufficiently skewed to kill neurons other than Purkinje cells. Doctor Wiznitzer

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[288] H. Monnerie, *et al., Effect of Excess Extracellular Glutamate on Dendrite Growth From Cerebral Cortical Neurons at 3 Days In Vitro: Involvement of NMDA Receptors*, J. NEUROSCI. RES. 74: 688-700 (2003) ["Monnerie"], filed as Snyder Pet. Ex. 228. Excess glutamate caused dendrite injury, a precursor to cell death in cerebellar ischemia. *Id.* at 697.

noted that seizures in ASD generally occur in adolescence or young adulthood, years after the onset of ASD's core symptoms. If excess glutamate caused both conditions, seizures should begin at the same time as onset of the core symptoms. Snyder Tr. at 698-700. Even if there is a gradient effect, with increasing levels of glutamate triggering seizure onset, the theory does not explain why those with ASD most prone to developing seizures are those with lower degrees of mental functioning. Snyder Tr. at 699A-700.

(c) Stage 3.

Stage 3 of Dr. Kinsbourne's revised theory incorporated the over-arousal theory he first suggested in his 1980 article. However, he cited additional references in support of this theory, including one book (Baron),[289] and two articles (Liss[290] and Vlsootsak[291]). In essence, Dr. Kinsbourne attributed many of the behaviors in the impaired social interaction domain and the restricted, repetitive, and stereotyped behavior domains of ASD to over-arousal or overexcitation in the brain. His citations provided little or no support for the proposition that these behaviors can be attributed to glutamate excess. None of the articles he cited discussed glutamate levels. Some clinical evidence (the page from Baron's book) points to higher basal heart rates in a group of patients with ASD, but even that evidence was in conflict with other research finding lower parasympathetic responses in individuals with autism. *See* Snyder Res. Ex. DD at 2. Anxiety is common among children with ASD, but there is no evidence filed demonstrating that anxiety disorders in ASD (or in typically developing children) are caused by abnormal GABA or glutamate levels. Snyder Tr. at 707.

At best, Dr. Kinsbourne puts forth an interesting theory, albeit one with no clinical support. He argues for a virally-caused inflammation, but the evidence, discussed in Section VII, below, indicates that measles virus in the brain causes an entirely different type of damage than is found in autism. Other viral brain infections, such as herpes encephalitis, likewise cause damage different from that observed in the brains of those with ASD. He postulates that a glutamate excess is causal of the behaviors observed in those with ASD, but there is no evidence of such an excess in those with ASD. His efforts to reconcile a glutamate-GABA imbalance sufficient to cause ASD's behavioral symptoms in early childhood, but insufficient to cause seizure disorders until later in the

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[289] M. Baron, *et al.*, eds. STRESS AND COPING IN AUTISM, Oxford University Press, Inc. (2006), filed as Snyder Pet. Ex. 216. Petitioners filed only one page from the book, in addition to the title and publication information pages. That page (53) discussed studies comparing cardiac responses from children with ASD in stressful situations, noting higher beats per minute in the ASD subjects, as compared to a typically developing group at baseline and during stress. The page provided does not support Dr. Kinsbourne's statement that higher-functioning individuals with ASD seem overaroused.

[290] M. Liss, *et al.*, *Sensory and attention abnormalities in autistic spectrum disorders*, AUTISM 10(2): 155-72 (2006), filed as Snyder Pet. Ex. 109.

[291] J. Vlsootsak, *et al., Fragile X Syndrome: An Update and Review for the Primary Pediatrician,* CLIN. PEDIATRICS 44: 371-81 (2005), filed as Snyder Pet. Ex. 231.

disease process does not explain why seizures are more often found in those ASD patients with the most severe levels of mental retardation. Doctor Kinsbourne takes bits and pieces of articles and studies and attempts to weave a causation theory from them.

The starting point for Dr. Kinsbourne's stages is inflammation caused by a persistent measles virus infection of the brain. If the starting point is unsupported, the theory of measles vaccine causation collapses. As the next section of this opinion sets forth, there is no evidence the measles virus causes inflammation or any other brain pathology found on autopsy of ASD patients. A great deal is known about what persistent measles virus does when it reaches the brain, and its effects do not resemble autism. The nature of the measles virus and its known effects are discussed in Parts B and C, below.

(2) Doctor Corbier's Theory.

Like Dr. Kinsbourne, Dr. Corbier found the timing for development of ASD symptoms to be important in determining the cause. Because regressive autism manifests later in life, he found it more likely that environmental factors played a role in causing the condition. Hazlehurst Tr. at 269A. He acknowledged the role of genetics in predisposing a child to autism, but believed external environmental factors also played a role in regressive autism. Hazlehurst Tr. at 270A. He stated that "MMR has been implicated in a subset of children with autism," defining the subset as those children who developed normally, had the MMR vaccine, and then regressed and developed other symptoms of autism, coupled with either gastrointestinal symptoms or immunologic problems.

In support of this opinion, he referred to "several studies" implicating measles virus as a contributing factor to both gastrointestinal and neurologic problems. Hazlehurst Tr. at 271A-72A. He identified studies by Uhlmann, Kawashima, Bitnun (sometimes identified in the record as "Bitoun"), and Bradstreet as those upon which he relied.[292] Hazlehurst Tr. at 273A-74A. He indicated that the case report by Bitnun[293] referenced autistic symptoms before inclusion-body encephalitis was diagnosed. Hazlehurst Tr. at 274A. In this, Dr. Corbier was clearly misinformed. The Bitnun article did not describe any symptoms consistent with autism, and upon admission to the hospital, the 21 month old child whom the article discussed was described as "previously healthy" with a two-week history of irritability and occasional vomiting. Bitnun, Cedillo Pet. Ex. 61, Tab K at 855.

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[292] Studies authored by Uhlmann and Kawashima are discussed at some length in Section VII. There were two studies by Bradstreet. The 2003 article concerning mercury and autism was discussed in Section V, Part C; the 2004 article is discussed in Section VIII.

[293] A. Bitnun, *et al., Measles Inclusion-Body Encephalitis Caused by the Vaccine Strain of Measles Virus*, CLINICAL INFECTIOUS DISEASES 29: 855-61 (1999) ["Bitnun"], filed as Cedillo Pet. Ex. 61, Tab K.

Doctor Corbier apparently did not require persistence of measles virus in order to establish causation. Instead, he indicated that the virus could be cleared after triggering an autoimmune disorder. Hazlehurst Tr. at 280A, 326A-27A. He noted that gastrointestinal disorders, such as celiac disease, could trigger neurological problems, including seizure disorders. Hazlehurst Tr. at 281A-82A. His support for an autoimmune cause of autism were articles by Zimmerman, Ashwood, Gupta, and Singh.[294] Hazlehurst Tr. at 426A.

If there were no evidence of persistent measles virus, Dr. Corbier might still opine in favor of vaccine causation based on an autoimmune reaction and the presence of autoantibodies. Hazlehurst Tr. at 416A-17A. In the absence of MMR and thimerosal exposure in a child with regressive autism, Dr. Corbier would look for other environmental triggers. Hazlehurst Tr. at 420A-21A. He testified that "any neurotoxic agent that the developing brain is exposed to in the right individual...someone that has the right genetic predisposition, can result not only in the development of autism, but could also contribute to other conditions, neurologic or nonneurologic." Hazlehurst Tr. at 421A.

Doctor Corbier did not discuss in any detail the how he believed the MMR vaccine could cause ASD. Instead, he referred to similarities between ASD symptoms and known complications from measles virus, specifically an autoimmune encephalitis and a disease caused by persistent measles virus in immunologically compromised recipients. Both of these conditions are discussed in some detail, below. However, neither condition resembles autism in any material way. None of the researchers he identified as working in the field of the immunology of autism has suggested MMR causation of their often-conflicting immune system findings.[295]

Much of Dr. Corbier's opinion focused on the temporal relationship between the MMR vaccination and regression, rather than a medical theory of causation. He did not address the high probability of coincidence in this temporal relationship; with most children having received an MMR vaccination in the six months before autism's

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[294] As Dr. Corbier was not specific about which of the articles by these authors that he relied upon, anything more than a review of the evidence concerning immune system parameters and possible autoimmunity in children with ASD, as discussed in Parts D and E, below, is difficult. In summary, the evidence, including articles by the researchers Dr. Corbier identified, indicates that there are some unusual immune parameters in some of those with ASD, but no evidence that it is an autoimmune condition. There is no evidence that the immune system findings are related to ASD's pathogenesis. *See generally*, IOM 2004 Report, Cedillo Res. Ex. JJ, at 131.

[295] Doctor Zimmerman's report clearly indicated that he did not believe the MMR vaccine to be causal of autism. Cedillo Res. Ex. FF at 4. The papers listing Dr. Gupta as the primary author were published in 1998 and 2000 (filed as Cedillo Res. Ex. R, Tab 22 and Snyder Pet. Ex. 181) took no position on vaccine causation. Doctor Ashwood's two articles were both discussed at some length. The Ashwood 2006 article reflected the lack of consistency in the research into immune system parameters in children with ASD. Doctor Singh's research came closest to suggesting some connection, but his own findings were inconsistent and criticized. *See* discussion in Parts D and E, below.

symptoms are most commonly noted, most children with ASD will have this temporal relationship.

I did not find Dr. Corbier's testimony enlightening or persuasive. It was superficial, relied heavily on questionable interpretations of research (such as his statement that autism is an autoimmune condition), and made sweeping statements of "fact" without support. He did not provide a reliable medical theory that supported vaccine causation. His opinion was not grounded in scientific methodology and procedure, merely subjective belief and unsupported speculation. Much of his testimony relied upon Unigenetics' reports of finding persistent measles virus in the gut or brain of children with ASD, reports I do not find to be reliable, for the reasons set forth in Section VI, Part G.5, and Section VIII, Part E.5, below.

B. Measles Virus.

1. Measles Virus Composition.

Measles virus belongs to a family of viruses known as paramyxoviruses and, more specifically, to the subgroup called morbilliviruses. Morbilliviruses are species-specific.[296] Cedillo Tr. at 715-16, 2754A-55. The primate strain of measles virus enters cells using receptors that are not naturally present in animals other than primates.[297] Cedillo Tr. at 2753-54A.

The measles virus is a single-stranded RNA[298] virus. Cedillo Tr. at 603A, 712-13; Cedillo Pet. Tr. Ex. 7 at 7. RNA viruses are unstable, and need to replicate constantly in order to maintain themselves.[299] Because of this instability, RNA viruses are

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[296] The term "species specific" means that the morbillivirus that causes measles in humans and primates is a different virus from those that infect canines (canine distemper virus, which is neurotropic), seals (phocine virus), and cattle (rinderpest virus). The diseases caused by morbilliviruses are somewhat similar across species (Snyder Tr. at 309A), but not identical. The effects of a morbillivirus specific to another species cannot be analogized to the effects in humans. Cedillo Tr. at 715-16, 2754A-55. Although Dr. Kennedy analogized measles' neurologic effects to those of canine distemper virus, the rinderpest virus is the morbillivirus most similar genetically to the measles virus. The rinderpest virus is not a neurotropic morbillivirus. Snyder Tr. at 309A, 358A-59A.

[297] Transgenic mice containing human cell receptors have been created. However, the viral infection route and spread in transgenic mice does not mimic the replication and spread of the virus in humans. Cedillo Tr. at 2753-54A.

[298] "RNA" is an abbreviation for ribonucleic acid, a molecule that is discussed in more detail later in this opinion. DORLAND'S at 1638.

[299] Doctor Kennedy testified that the measles virus could persist in a host without continued replication (production of new virus). Cedillo Tr. at 731A-32A. He did not provide any support for this statement. In view of the greater experience of Dr. Rima with the measles virus, I find Dr. Rima's testimony that the virus must continue to replicate in order to survive to be more persuasive than Dr. Kennedy's testimony that it does not. Snyder Tr. at 837A-38A, 911.

substantially less persistent than DNA[300] viruses. Snyder Tr. at 837A-38A; Cedillo Tr. at 603A-604A.

Once the measles virus enters a cell, it hijacks the host cell's own machinery to assemble more copies of itself. Cedillo Tr. at 728. The RNA molecules produced are translated into proteins. Once concentrations of the proteins are high enough, the proteins travel to the cell surface, where they are assembled into new virions.[301] These copies of the full length virus are made into the nucleocapsid,[302] which binds to proteins on the cell surface. The virus spreads from cell to cell in a process called budding, in which the virus uses a part of the host cell membrane to create its own envelope. Cedillo Tr. at 1822-25A.

2. Infectious Mechanisms.

An illustration from Fields' VIROLOGY[303] demonstrates the replication of measles virus in wild-type infections.[304] The virus is primarily transmitted from person to person through inhalation of aerosol droplets.[305] It is carried from the respiratory tract to the lymph nodes, and spreads through the blood in what is called a cell-associated viremia. The virus primarily infects lymphocytes and monocytes in the blood, as well as infecting tissue in the lymph glands. Cedillo Tr. at 2751-52. It is one of the most infectious viruses known. Cedillo Tr. at 2750

Once in the blood, the virus spreads widely in the body. The skin rash characteristic of measles is evidence that the virus has spread to the skin. There may also be liver or cardiac abnormalities caused by the virus. It spreads to gut tissue and to lymphoid cells, but it has a special affinity for endothelial and epithelial cells. Because these cells exist in many organs, the virus can be found in any organ containing them, and, thus, it is considered a systemic virus. Cedillo Tr. at 2751-52; 2755-56.

Doctor Kinsbourne testified about several characteristics of the measles virus.

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[300] "DNA" is an abbreviation for deoxyribonucleic acid. DORLAND'S at 557. Herpes, Epstein-Barr and varicella viruses are examples of DNA viruses that persist in humans. Snyder Tr. at 837A-38A.

[301] A virion is a complete virus, capable of surviving and infecting a living cell. DORLAND'S at 2041.

[302] A nucleocapsid is a unit of viral structure, consisting of a protein coat enclosing the nucleic acid. DORLAND'S at 1282.

[303] Cedillo Res. Ex. R, Tab 18.

[304] Cedillo Res. Tr. Ex. 23 at 1.

[305] Even after infection with the wild-type measles virus, it takes several days for a sufficient viral load to be established in the respiratory tract to make a person infectious to others. Cedillo Tr. at 2778A.

He indicated that the virus is lymphotropic,[306] enterotropic,[307] neurotropic,[308] and immunosuppressive. Cedillo Tr. at 1067A-68.

The measles virus enters a cell through receptors on the cell's wall. Cedillo Tr. at 1822-24A. Within immune system cells, the wild measles virus uses a cell receptor called SLAM, or CD150. Doctor Kennedy incorrectly described the CD46 receptor as one used by the wild-type measles virus. It is the preferential receptor for vaccine strain measles virus, not the wild-type measles virus. Cedillo Tr. at 1822-23A, 2774-75. The cell receptor in epithelial or endothelial cells is not yet known. Cedillo Tr. at 2755.

Measles is a completely cell-associated virus. There is little evidence indicating that it lives outside of cells. Although it moves from cell to cell, it does so very efficiently, entering a new cell almost instantaneously after leaving the previous cell. For this reason, attempts to isolate the virus from plasma have proven unsuccessful; the virus is only isolated from cells. Snyder Tr. at 950-51A. Wild-type measles virus is highly infectious *in vivo*, but is difficult to grow in tissue culture. Cedillo Tr. at 2750-51.

C. Vaccine Strain Measles Virus.

The virus used in the MMR vaccine contains the same genes and proteins as the wild-type virus. Cedillo Tr. at 714A. To distinguish between the two viruses, it is necessary to examine the sequence in which nucleotides appear in their genes. Cedillo Tr. at 483A, 635A, 667. The vaccine strain virus is attenuated, meaning that it has lost its virulence. Cedillo Tr. at 2774. The attenuated virus does not replicate as strongly as the wild type virus. Cedillo Tr. at 771, 2775-76.

The measles vaccine was originally grown in monkey kidney cells and was then attenuated by passing it through chicken embryo fibroblasts.[309] Snyder Tr. at 831-32A;

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[306] "Lymphotropic" means having an affinity for the lymph glands. Cedillo Tr. at 1067A. Doctor Griffin agreed that the virus is very lymphotropic. Cedillo Tr. at 2751.

[307] "Enterotropic" means having an affinity for the lining of the digestive system. Cedillo Tr. at 1068. Doctor Griffin explained that the virus has an affinity for lymphoid tissue and endothelial cells anywhere they are found, but that the virus does not preferentially select gut tissue. Both lymphoid tissue and endothelial cells are found in the gut. Cedillo Tr. at 2755-56. I accept Dr. Griffin's testimony as correct.

[308] "Neurotropic" means having an affinity for nervous tissue. Cedillo Tr. at 1068. Doctor Griffin indicated that, in children dying of acute measles infection, the virus was only located in brain endothelial cells, not in brain tissue itself. In the rare neurological illnesses associated with persistent measles virus, a characteristic measles inclusion body can be seen on autopsy. Cedillo Tr. at 2756-57, 2789A.

[309] Doctor Kennedy testified that the vaccine strain measles virus was attenuated in monkey kidney cells and tested for virulence in mice. Cedillo Tr. at 714A. Doctor Ward testified that this was incorrect. The virus was attenuated in chicken embryo fibroblasts, and neurovirulence testing was performed on primates. Cedillo Tr. at 1818A-20A. I accept Dr. Ward's testimony as correct.

Cedillo Tr. at 2774-75. This adaptation means that it is unable to grow as effectively as the wild-type disease strain virus in human cells. Because the attenuated virus does not replicate as readily in human cells, the amount of viremia is almost undetectable, when compared to the wild-type virus.[310] It is very difficult to get sufficient viremia with vaccine strains to detect the virus in the blood. Cedillo Tr. at 2774-78A.

The clinical response to the vaccine virus differs from the response to the wild-type virus in that the vaccine strain generally does not cause disease, and the vaccine virus is not transmissible from one person to another. Cedillo Tr. at 2778A. The lack of virulence is measured by clinical response, and it is not based on knowledge of which mutations are relevant to the attenuation. Determining which mutations are relevant to attenuation is one of Dr. Rima's research interests. Snyder Tr. at 832A.

All measles vaccines come from the Edmonston strain of the measles virus. Snyder Tr. at 833A. The original vaccine virus produced from this strain was not well attenuated, and was later withdrawn and replaced with the far more attenuated current version. Cedillo Tr. at 1894A-96A. The original vaccine occasionally caused Koplik spots,[311] but the current vaccine does not cause them. Clinically apparent side effects from the vaccine strain virus include rare and transient episodes of thrombocytopenia and, more commonly, fever. The current vaccine has been administered for at least 35 years. Snyder Tr. at 833A.

D. Immune Response to Measles Virus.

1. Immune Response to Wild-Type Measles Infections.

As an immunosuppressive virus, wild-type measles virus presents a major challenge to the immune system, regardless of whether those exposed develop complications from the virus. Cedillo Tr. at 1887A, 2745. In measles infections, the immune system is actively involved in fighting the measles virus, and does not respond normally to other pathogens. Thus, most measles-related deaths are the result of bacterial pneumonia or other opportunistic infections, rather than from the measles disease itself. Cedillo Tr. at 1889-90, 2767-69. The period of immunosuppression begins at 9-15 days after exposure to the virus, and continues for approximately two to three months after recovery from measles disease.[312] Cedillo Tr. at 2798-99. There

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[310] This difference is illustrated in Cedillo Res. Tr. Ex. 23 at 6.

[311] Koplik's spots are pathognomonic of measles. Nothing else causes them. Snyder Tr. at 971A.

[312] Doctor Kennedy testified that the period of immune suppression from wild-type measles virus lasts from three to six months. Cedillo Tr. at 717-18A. Other testimony established that the longer period applied only in patients who were immunosuppressed at the time of the measles infection. Cedillo Tr. at 1889-91 (Dr. Ward) and 2799-2802 (Dr. Griffin); Snyder Tr. at 831-36A (Dr. Rima). I found the testimony of Drs. Ward, Rima, and Griffin to be more persuasive than that of Dr. Kennedy, given their greater experience with, and decades of research into, measles virus.

may be some changes in cytokine levels that last longer than three months, but they are not clinically relevant. Cedillo Tr. at 1881-82A, 2798-02.

After infection, DC pick up the virus and carry it to the lymph nodes where they present the virus to cells that are capable of responding to it, primarily T cells. In the first few days of the infection, the virus is replicating and newly infected cells are going out into the bloodstream. At the same time, the body is also fighting the replicating virus, first by CD4 T cells, and later by CD8 T cells. Cedillo Tr. 2762-63. In the presence of the measles virus, these cells and the B lymphocytes that specifically recognize the measles virus are stimulated to reproduce in great numbers. Cedillo Tr. at 2763-64.

The B lymphocytes that are stimulated first make IgM antibodies, which restrict the spread of the virus. Through class switching, some B cells begin making IgG, the long-term response to measles. This process is T cell dependent and involves both class switching and affinity maturation. Affinity maturation confers life-long immunity to measles virus, because any measles virus encountered thereafter will be defeated by B cells previously selected as those best able to recognize and fight the virus. Cedillo Tr. at 2762-67.

In the immune response to measles virus, the roles of CD4 and CD8 T cells are complicated. The CD8 cells produce a Th1 response, producing cytokines such as IFN-γ and IL-2 during the acute phase of the infection. Once the acute infection is over and the viremia is cleared, the CD4 cells produce cytokines such as IL-4 and IL-13 that induce a mature antibody (Th2) response. Thereafter, regulatory T cells produce IL-10 cytokines to help calm the immune response. Cedillo Tr. at 2772-74, 2802-04A, 2813A.

The time frame in which the Th2-deviated response occurs would roughly correspond to the period of maximum viremia after infection with the measles virus. Cedillo Tr. at 1880. This Th1 to Th2 shift in immune response does not mean that the immune system is imbalanced or that the response is maladapted. Cedillo Tr. at 1878A-79B. The skewing of the immune system to a Th2 response may be part of the reason for the immunosuppression seen in measles infections, but this is an area in which medical knowledge is lacking, and studies are difficult to conduct. Cedillo Tr. at 2805-07.

Clinically, children who recover from measles infection appear to resume normal immune system parameters relatively soon after infection. An article[313] by Aaby examined immune system functioning after wild-type measles infections in Africa. In the first two months after infection, children who had contracted measles had no significant differences in lymphocyte levels as compared to children who did not

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[313] P. Aaby, *et al., No persistent T lymphocyte immunosuppression or increased mortality after measles infection: a community study from Guinea-Bissau*, PEDIATR. INFECT. DIS. J. 15(1): 39-44 (1996), filed as Snyder Res. Ex. V, Tab 4.

contract the disease, although the percentage of CD8 cells tended to be higher among those who had contracted the disease. The study found no signs of suppression of CD4 cells in the case children during the two months after infection; in fact, CD4 cell counts were higher in the case children than in the control children.

2. Immune Response to Vaccine Strain Virus.

In contrast to the wild-type virus, the measles vaccine virus does not cause any clinically relevant immune suppression. Cedillo Tr. at 1801A-03A; Snyder Tr. at 831, 969A-70A. Unlike the immune response to the wild-type virus, there is simply a period of immunologic abnormalities with regard to laboratory values. However, the abnormalities do not result in any increased susceptibility to disease.[314] Cedillo Tr. at 1890-91, 2800A-02. Doctor Zweiman described this as a "moderate transient decrease in cell-mediated immunity that is expressed by delayed hypersensitivity skin testing," along with a decrease in cellular reactivity to certain antigens. Humoral response (antibody formation) remains vigorous and normal. Snyder Tr. at 590A. Doctor Griffin indicated that the immune response to the vaccine virus should not be characterized as immunosuppression, but rather as some immunologic changes coincident with inducing the immune response to measles. Cedillo Tr. at 2781. Doctor Zweiman also testified that there is no clinically relevant immunosuppression caused by the measles vaccine. Snyder Tr. at 590A-91A.

Doctor Kennedy disagreed with the measles experts and immunologists on this point, testifying that the measles vaccine virus could cause sufficient immunosuppression to allow the virus to persist. Cedillo Tr. at 760. However, on cross-examination, he could not quantify the level of immune suppression that the vaccine strain virus could cause, or cite to any reference materials indicating the MMR vaccine virus could persist as the result of the virus's own immunosuppressive ability. Cedillo Tr. at 765-68. Testifying in *Snyde*r, he continued to dodge the question of what medical literature supported his claim that the vaccine virus could cause sufficient immune suppression to allow the virus to persist. Respondent's counsel asked the question several times (Snyder Tr. at 372A, 373A, 374A), until Dr. Kennedy finally referred to an article discussing neurological problems, not immune suppression, after the vaccine. He reasoned that "MMR can cause immunosuppression, MMR can cause neurologic events. Therefore, immunosuppression could play a role in those events using a, A is to B, to B is to C so A + B = C." Snyder Tr. at 375A.

Doctor Kennedy's somewhat skewed logic does not substitute for respondent's experts' 50 years of experience with the attenuated virus vaccine. With regard to the ability of the vaccine strain virus to cause clinically relevant immune suppression, I found the testimony of Drs. Griffin, Ward, Zweiman, and Rima more persuasive than that of Dr. Kennedy, given their greater experience with, and research into, measles

[314] Doctor Kennedy testified the period of immune suppression from measles vaccine virus would last from three to six months, the same time frame as that of the wild-type virus. Cedillo Tr. at 718.

virus and immunology. Although this was an area of disagreement among the parties, Dr. Griffin's testimony that the response to the vaccine virus was not immunosuppression, merely a period of immunologic changes, was more persuasive. Cedillo Tr. at 2779A-81A. She was the witness most qualified to opine on this topic, and her testimony was buttressed by that of Drs. Ward and Rima. Cedillo Tr. at 1896A, 2778A-81A; Snyder Tr. 590A-91A, 831A, 969A-70A.

A positive IgG measles titer reflects that an individual has been exposed to measles virus in some form. A positive IgG measles titer and a negative IgM titer reflects both exposure to and clearance of the virus, whether vaccine strain or wild-type. Cedillo Tr. at 2217A-18A. In order to produce an IgG response to measles virus, both CD4 T cells and B lymphocytes must be working properly. The IgG response indicates the immune system is functioning properly with regard to the measles vaccine. Cedillo Tr. at 2781A-82A.

Following measles immunization, transient Th2 skewing occurs. This skewing does not appear to have any clinical significance. Cedillo Tr. at 1869A. Doctors Ward and Griffin were the first to demonstrate a Th2 response to wild-type measles and to measles vaccine. Cedillo Tr. at 1812A. The individuals who displayed this decreased hypersensitivity (a decrease in cell-mediated immunity and reactivity to certain antigens) were clinically fine, and there was no evidence of any increase in infections over the five to six weeks during which the decreased hypersensitivity continued. Humoral immune response, including that to the vaccine virus, was perfectly normal. Snyder Tr. at 590-91A.

The vaccine virus also results in transient lymphopenia,[315] probably due to the involvement of lymphocytes in the induction of the immune response in the lymph nodes. Cedillo Tr. at 2809-10A. Rarely, it may also cause transient thrombocytopenia. Snyder Tr. at 833A. In about 10% of children receiving the vaccine, a rash develops, and most children also develop a fever. About 5-15% of children develop a fever of 103 degrees or higher after vaccination, but this fever rarely has long-term clinical ramifications. Cedillo Tr. at 2206, 2779A. The Vaccine Injury Table recognizes that the measles vaccine can cause anaphylaxis, encephalopathy or encephalitis, thrombocytopenia purpura, and, in an immunodeficient recipient, vaccine strain measles viral infection. *See* 42 C.F.R. § 100.3(a).

Most other vaccines are prohibited in the month after a measles vaccine, other live-viral vaccines, or even after steroid treatment, because the immune response to another vaccine might be reduced. The antiviral state initiated by the vaccine virus might decrease the ability of other vaccines to induce an immune response, but there is no concern that the subsequent vaccines might cause illness during a period of alteredor suppressed immunity. Cedillo Tr. at 1890-91.

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[315] Lymphopenia is a decrease in the number of circulating lymphocytes. Cedillo Tr. at 2809-10A; DORLAND'S at 1080.

Doctor Ward testified that, as a general rule, if a wild-type virus can cause a problem, the vaccine virus can also cause the problem, albeit in a milder or more attenuated form. Cedillo Tr. at 1894A-96. Doctor Griffin agreed with this principle, testifying that the complications from measles vaccine would be a diminished version of those present in wild-type virus infections, but would not include new complications, ones not found in wild-type virus infections. Cedillo Tr. at 2779A-81A.

E. Petitioner's Theory Regarding Immune Suppression in Response to MMR.

In essence, petitioners contend that children with regressive autism have both primary and secondary immune system defects. The primary defect is a genetic predisposition resulting in an immune "dysregulation"[316] prior to the MMR vaccination. The secondary defect, allegedly caused by the effect of TCVs and the measles vaccine virus on the immune system, ostensibly results in a suppression of immune response and an ineffective attempt to clear the measles vaccine virus from the body. This section discusses the evidence for immune system malfunctions in children with ASD, and the immunological effects of measles vaccine virus on children with ASD and on those with immune system defects.

1. Evidence that Children with Autism have Malfunctioning Immune Systems.

Petitioners' arguments on this point were blatantly circular. Evidence that a child had autism was used to demonstrate that the immune system of the child was malfunctioning.[317] Evidence that a child had a malfunctioning immune system was used to demonstrate why the virus persisted to cause autism. There was no evidence introduced that children with autism have genetic defects that alter their immune response to viruses or other pathogens. There was evidence that some of those with ASD have unusual immune system profiles, although these findings were not consistent. There was no evidence that these profiles have any clinical significance.

Doctor Byers opined that the impaired immune systems of autistic children render their bodies unable to clear live virus vaccines, including MMR. Cedillo Tr. at 935-39. As a result of the children's impaired immune systems, the measles vaccine virus can cause an exaggerated inflammatory response. Cedillo Tr. at 952-53. However, Dr. Byers offered no convincing support for the proposition that autistic children have immune system weaknesses, genetically-caused or otherwise.

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[316] Petitioners' theory does not depend on establishing an exact cause for the postulated immune "dysregulation." Petitioners can prevail, without demonstrating any effect of TCVs on the immune system, if they can demonstrate that the measles virus persists. However, a malfunctioning immune system makes the persistence of the measles virus more likely, regardless of the cause of the malfunction.

[317] Doctor Byers made precisely this argument: "One has to say that genetically, an autistic child has an immune system that is innately prone to being damaged, and it appears that the main place that it is going to be damaged is by an aberrant reaction to environmental stimuli." Cedillo Tr. at 935.

According to Dr. Byers, an Ashwood article[318] regarding immune response in autism provided a good summary of what was known about the immune status of autistic children. Cedillo Tr. at 891A-93A. The Ashwood 2006 paper described a number of studies finding various, and sometimes contradictory, immune system abnormalities in autistic children. It noted that many of the studies compared autistic children to adult controls and failed to control for the medication status of the autistic children, which could be a significant confounding factor. The authors also noted a possible patient selection bias in the studies. They speculated that the discordant results from some studies may "potentially reflect different autism behavioral phenotypes." Ashwood 2006 Cedillo Pet. Ex. 61, Tab C, at 4. Ashwood's conclusion noted: "Within the literature describing immune-based studies in ASD, there are a number of discrepancies and unreplicated reports. Numerous studies report apparently conflicting results, and thus far, no consensus about the described immune findings has been reached." *Id.* at 11. At best, this article suggested that immune dysfunction may play a role in subgroups of patients with autism, without actual evidence that the discordant results truly reflected subgroups of ASD. It offered no support for the proposition that the MMR vaccine caused immune suppression or for vaccines as causative agents in autism. Cedillo Tr. at 1816-17.

Doctor Byers testified that most of the reports found that autistic children have abnormal innate immune responses, particularly overly reactive inflammatory responses. She referred to the Jyonouchi study[319] as demonstrating abnormal levels of three proinflammatory cytokines in ASD patients: TNFa, IL-1β and IL-6. Cedillo Tr. at 889A-90A. The article did demonstrate higher levels of these cytokines in the autistic children studied, compared to a control population of adults. However, it drew no conclusions regarding cause and effect of the higher cytokine levels, and it noted that values two standard deviations above the control values were also found in a number of healthy siblings of the autistic children. Jyonouchi 2001, Cedillo Pet. Ex. 61, Tab MM at 175-76.

According to Dr. Byers, the Vargas study[320] demonstrated that autistic children had abnormal activation of the microglia and astroglia (astrocytes), dendritic-like cells in the brain, resulting in inflammation in wide areas of the brain. Cedillo Tr. at 890A. Her testimony correctly reflected the findings from that article, but drew the conclusion,

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[318] P. Ashwood, *et al.*, *The immune response in autism: a new frontier for autism research*, J. LEUKOCYTE BIOLOGY 80: 1-15 (2006), filed as Cedillo Pet. Ex. 61, Tab C ["Ashwood 2006"].

[319] H. Jyonouchi, *et al., Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression,* J. NEUROIMMUNOLOGY 120: 170-79 (2001), filed as Cedillo Pet. Ex. 61, Tab MM ["Jyonouchi 2001"]. Doctor Byers did not identify which of the several articles authored by Jyonouchi she meant, but from context, it appears that she was referring to this one. However, later in her testimony (Cedillo Tr. at 893A), she mentioned articles by Jyonouchi written in 2000 and 2006. No articles by Jyonouchi published in 2000 or 2006 were filed.

[320] Vargas 2005, filed as Cedillo Pet. Ex. 61, Tab MMM.

unsupported by the research, that the innate immune system activation was the result of an infectious agent.

Doctor Byers also testified that the Ashwood 2004 paper[321] found elevated numbers of CD3 cells in the gut of autistic children with chronic bowel disease. These cells are part of the adaptive immune system. Cedillo Tr. at 891A-92A. When the innate immune system fails to clear an invading pathogen, the adaptive immune system activates. She testified that these immune system findings were indicative of a chronic infection in the autistic children studied. Cedillo Tr. at 891A. The Ashwood 2004 paper actually found similar CD3 cell counts in both the ASD children, referred for gastrointestinal complaints, and in the typically developing children, referred for inflammatory bowel disease. The study found no correlation between the degree of inflammation in the children with ASD and the proportion of cytokine-positive CD3 cells. Ashwood 2004, Cedillo Pet. Ex. 61, Tab B, at 668-69.

Doctor McCusker disagreed with Dr. Byers regarding both the evidence of immune system dysfunction in those with ASD and any causal role of immune dysfunction in autism. She testified that autism was once thought to be related to immune dysfunction, but this hypothesis is no longer generally accepted. The initial article suggesting a role for immune dysfunction in causing autism, published in 1976, was based on a case report. Several studies have since tried to evaluate immunity in autism, but have returned inconsistent findings. Cedillo Tr. at 2207; Cedillo Res. Ex. Z at 2. In her own experience, having tested the immune profiles of approximately 100 children with autism over eight years, she found only one such child with an immune deficiency. She did not believe that immune deficiencies or immune mechanisms play any role in the development of autism. Hazlehurst Tr. at 585A-86A.

Doctor Byers' position is simply unsupported by the evidence adduced. As the Ashwood 2006 survey article indicated, studies showing immune dysfunction in autism were frequently contradictory and most suffered from some defects.[322] However, Dr. McCusker's testimony did not address the evidence from the Vargas study, that the brains and CSF of autistic individuals demonstrated some degree of inflammation associated with an innate immune system response. Whether this is a cause of autism, or simply an effect of autism, is not yet established. Certain of Vargas's findings suggest that the inflammation may be an effect. Vargas found that tumor growth factor-β1 (an anti-inflammatory cytokine involved in tissue remodeling after injury) was one of the most prevalent cytokines found in brain tissues of autistic individuals. Vargas 2005, Cedillo Pet. Ex. 61, Tab MMM, at 79. Doctor Zimmerman, a co-author of this paper, noted that, in spite of the findings of immune activation in autism, there was no

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[321] Cedillo Pet. Ex. 61, Tab B. Doctor Wakefield was a co-author of this article.

[322] *See also* I. Krause, *et al., Brief Report: Immune Factors in Autism: a Critical Review*, J. AUTISM DEV. DISORD. 32(4): 337-45 (2002), filed as Cedillo Pet. Ex. 59, Tab G. This article reviews studies reporting various immune system abnormalities in children with autism, noting that many studies have contradictory results.

evidence suggesting an infection. Cedillo Res. Ex. FF at 3.

2. Evidence Regarding an Altered Immune Response to Measles Vaccine.

Petitioners contended that children with ASD have aberrant immunologic responses to the measles vaccine, which permit its persistence in gut and brain, but also include unusual levels of measles antibodies and myelin basic protein ["MBP"] autoantibodies.[323] The evidence proffered to show altered immune response was countered by other evidence reflecting no significant differences in immune response between children with and without ASD. Additionally, evidence demonstrating that measles vaccines are routinely given to children with challenged or compromised immune systems, without harmful effects, undercuts the theory that the vaccine virus is immunosuppressive or leads to viral persistence.

The studies cited by Dr. Corbier, and other petitioners' experts, as evidence for an altered immune response to measles vaccine in children with autism, were inconsistent, and frequently their results were not replicated by other researchers. Summaries of the many differences in immune system parameters found in autism research may be found in the Ashwood 2006 article, Cedillo Pet. Ex. 55, Tab C, at 6 and in a slightly more recent article by Libbey.[324]

The Singh studies were illustrative of this problem. The initial Singh study[325] found no significant difference in measles antibody levels between children with ASD and typically developing controls. Subsequent studies by Singh showed significantly higher levels of measles antibodies in children with autism.[326] However, the more recent Libbey study, which involved age-matched controls,[327] found different results.

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[323] Myelin, the insulation that sheathes the brain's axons, can be damaged in a number of ways. When damaged, internal components of the myelin, which include myelin basic protein, leak out into the surrounding tissues. Some damage to myelin can be repaired by the oligodendrocytes. Snyder Tr. at 573. Myelin basic protein is one of the most abundant proteins found in myelin, comprising about 30% of the total protein in myelin. It has a very strong positive charge and is very alkaline. Snyder Tr. at 574A.

[324] J. Libbey, *et al., Are there altered antibody responses to measles, mumps or rubella viruses in autism?* J. NEUROVIROLOGY 13: 252-59 (2007) ["Libbey"] at 253, 255-56, filed as Snyder Res. Ex. BB. Doctor Fujinami was listed as the senior researcher on this study.

[325] V. Singh, *et al., Serological Association of Measles Virus and Human Herpesvirus-6 with Brain Autoantibodies in Autism*, CLIN. IMMUN. IMMUNOPATH. 89(1): 105-08 (1998), filed as Snyder Pet. Ex. 185.

[326] *See* V. Singh and R. Jensen*, Elevated Levels of Measles Antibodies in Children with Autism*, PEDIATRIC NEUROL. 28(4): 292-94 (2003), filed as Cedillo Pet. Ex. BB, Tab 87, and V. Singh, *et al., Abnormal Measles-Mumps-Rubella Antibodies and CNS Autoimmunity in Children with Autism*, J. BIOMED. SCI. 9: 359-64 (2002) ["Singh 2002"], filed as Snyder Res. Ex. J, Tab 7.

[327] Age-matching controls and subjects is important in comparing immune system parameters because these parameters change significantly with age. Libbey, Snyder Res. Ex. BB, pointed out that the Singh studies did not indicate age matching, nor did they report a mean age for cases and controls. This

The ASD case children were divided into two groups, classic onset and regressive onset. Typically developing children and children with Tourette's syndrome were used as controls. The researchers found no significant group differences in antibody titers to any of the pathogens tested (including measles virus), or in total IgG and IgM levels.[328] Moreover, although the Singh studies showed elevated antibody titers against measles or MMR vaccine in children with ASD, as compared to control children, this study did not.

The study also compared measles antibody levels to MBP autoantibodies in the ASD children. Unlike the Singh studies, they found no correlation between antibodies against measles and antibodies against MBP. The Singh 2002 authors speculated that the high MBP levels and high measles antibody titers that they found in autistic children evidenced an autoimmune process. However, other researchers found no evidence of cross-reactivity of antibodies to MBP and measles virus, indicating that if the MBP antibodies were evidence for an autoimmune process, the measles virus was not triggering that process. Libbey, Snyder Res. Ex. BB at 255.

At best, the evidence for an altered immune response to measles vaccine in children with ASD is contradictory. The Libbey study clearly contradicted the findings in the Singh studies and, unlike the Singh studies, accounted for a significant confounder, the mean age of the case children, as compared to the controls.

The evidence that children with compromised immune systems safely tolerate the measles vaccine also undercuts the argument that immune system dysfunction leads to an aberrant response to measles vaccine, contributing to the development of ASD. The World Health Organization recommends that asymptomatic children with known or suspected HIV infections receive measles vaccines. In fact, an extra dose, administered at six months of age, is recommended. *See* W. Moss, *et al., Immunization of children at risk of infection with human immunodeficiency virus*, BULL. WORLD HEALTH ORG. 81(1): 61-70 (2003), filed as Cedillo Res. Ex. BB, Tab 74. The incidence of adverse events after measles vaccination was not increased in HIV-infected children. *Id.*

Doctor Ward also discussed his personal knowledge regarding the use of the measles vaccine in Zimbabwe, an area with one of the highest rates of HIV in the world. Approximately 14,000 mothers and babies were recruited for a study of mother-to-child

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factor alone could account for the difference in antibody levels in ASD children as compared to controls in the studies. Older subjects had lower measles antibody levels than younger subjects in all the studied populations.

[328] Although the group differences in antibody levels were not statistically significant, more of the ASD children, in both the regressive and early onset groups, had very low or absent titers against the rubella virus than those in the two control groups. The individuals with very low or absent rubella titers were dropped from the analysis of variance. Libbey, Snyder Res. Ex. BB at 254.

transmission of HIV. About 1400 babies became HIV positive during the study. He noted the mortality rate of the HIV positive babies was almost 50% during the first two years of follow up, indicating a high rate of susceptibility to infections. All of these children, unless clinically ill at the time, received a monovalent measles vaccine at 9 months of age, and most also received TCVs. Despite receiving both TCVs and measles vaccine, this highly immunosuppressed population did not show any increase in reported cases of autism. Cedillo Tr. at 1804-07A.

In his report in *Snyder*, Dr. Kennedy discussed the high titer measles vaccine and increased mortality (from any cause) in girls, suggesting that this problem might have been caused by viral persistence or immune suppression.[329] Although this particular vaccine was never administered in the U.S, and, thus, could not be responsible for any U.S. cases of autism, Dr. Kennedy's expert report appeared to suggest that the high-titer vaccine problems provided a model by which a mechanism for vaccine causation of autism could be demonstrated. Snyder Pet. Ex. 30 at 5-6. At the hearing, he appeared to retreat from this position.[330] *See* Snyder Tr. at 362A-63A.

Another factor suggesting that measles vaccines do not cause clinically evident immune suppression is that measles vaccines are routinely administered to individuals with known prior tuberculosis exposure or even latent tuberculosis without activation or reactivation of the tuberculosis. Cedillo Tr. at 1883A-84A, 1887A-89.

I conclude that petitioners have failed to demonstrate that the MMR vaccine causes immunosuppression. There is no evidence that children receiving the vaccine have higher rates of infection in the months after vaccination than children who do not receive the vaccine. The immunosuppression seen after wild-type measles infections affects the body's ability to combat other infections, not measles itself. Given the conflicting state of the evidence regarding immune system parameters in children with ASD, the lack of persuasive evidence that children with ASD have an aberrant immune response to the vaccine, and the routine use of the vaccine in children with

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[329] *See* P. Aaby, *et al., High-Titer Measles Vaccination Before 9 Months of Age and Increased Female Mortality: Do We Have an Explanation?* SEMIN. PEDIATR. INFECT. DIS. 14(3): 220-32 (2003), filed as Snyder Res. Ex. V, Tab 1 and P. Aaby, *et al.*, *Five year follow-up of morbidity and mortality among recipients of high-titre measles vaccines in Senegal.* VACCINE 14(3): 226-29 (1996), filed as Snyder Res. Ex. V, Tab 3. These two articles discussed trials of high-titer measles vaccines in Africa. In the year following vaccination, more female recipients died after the high-dose vaccine than after the standard-titer vaccines. The 2003 study examined the hypotheses offered to explain the higher mortality rates, and concluded that an increased immunosuppressive effect of the high-titer vaccine was an unlikely explanation.

[330] In any event, the problems with the high-titer measles vaccine have no bearing on the role measles virus might play in causing ASD. Doctor Rima was part of a WHO team created to look at evidence of increased mortality in recipients of the high-titer vaccine. The increased mortality was on the border of statistical significance when boys and girls were considered together, but when female mortality was considered separately, there were statistically significant higher mortality rates in the girls receiving the high-titer vaccine. Doctor Rima testified that the data obtained from the review did not suggest that the increased mortality was due to any immune dysfunction. Snyder Tr. at 839A-41A.

compromised immune systems and latent tuberculosis, petitioners' argument that a subgroup of children with ASD responds to the measles vaccine in a manner different from both other children with ASD and typically developing children is unpersuasive.

This is not to say that the vaccine strain virus neither causes nor contributes to the development of diseases or disorders. The vaccine strain virus does cause problems, rare though they may be, which may be serious or even fatal. As a general principle, anything that the wild-type virus can cause can also be caused by the vaccine strain virus. Cedillo Tr. at 1894A-96A, 2779A-81A. The conditions commonly recognized as caused by either viral strain are discussed in Part F, immediately below.

F. Diseases Commonly Recognized as Caused by the Measles Virus.

1. Measles Infections.

Measles is a serious and highly infectious disease. It carries a significant risk of mortality, particularly in developing countries. In a 1988 measles epidemic in Guinea-Bissau, there was a 9.8% mortality rate in children under 3 years of age who contracted measles.[331] It is the second most common cause of vaccine-preventable death in children worldwide, killing 450,000 to 500,000 children annually. Cedillo Tr. at 2797.

The disease takes approximately one to two weeks to manifest. During the first 10 days after infection, a person is relatively asymptomatic. The virus is replicating, but there are no clinical signs of infection. During the prodromal period (the two or three days before the measles rash appears), probable symptoms include conjunctivitis, cough, and fever. Koplik's spots inside the mouth may be observed, permitting diagnosis before the rash appears. The skin rash occurs between nine and fifteen days after infection, marking the peak level of virus in the body, known as the period of maximum viremia.[332] Generally, the rash lasts for about three to five days, and appears as the adaptive immune system mounts its response to the virus.[333] The virus is generally cleared from the body by around 20 days after infection. Cedillo Res. Tr. Ex. 23 at 1; Cedillo Tr. 2751-53, 2758-59.

Although measles virus infects most tissues, it preferentially infects lymphoid and epithelial cells. In autopsies of acute measles virus victims, the virus was found widely distributed in the body but, in the brain, it was found only in vascular endothelial cells

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[331] *See* Aaby 1996,Snyder Res. Ex. V, Tab 4.

[332] The rash is caused by T cells attacking virus-infected cells in the skin. Cedillo Res. Ex. R at 3.

[333] Children who are immunosuppressed can get measles without getting the rash, which indicates that they are not generating a robust immune response to the measles virus. Cedillo Tr. at 2769-70.

(the lining of brain blood vessels), not in the brain tissue itself.[334] Cedillo Tr. at 2755-57.

Doctor Kinsbourne testified that diarrhea is a symptom of measles infection (Cedillo Tr. at 1137A), but Dr. Griffin testified that diarrhea is an uncommon symptom, primarily affecting those in developing countries, where exposure to other infectious agents, such as salmonella, is more common. Cedillo Tr. at 2760-61. I adopt Dr. Griffin's testimony as correct.

2. Other Diseases Caused by Measles Virus.

Doctor Kennedy testified that the measles virus and other viruses in the same family are "neurotropic" and can cause neurologic disorders and sequelae. He analogized measles virus to the canine distemper virus, which causes neurological symptoms in dogs, hypothesizing that the measles virus can cause the neurological symptoms related to autism in humans. Cedillo Tr. at 734-35A. Although measles virus can infect the brain, Dr. Kennedy's testimony was speculative, incomplete, and outside his area of expertise. In the millions of cases of measles treated worldwide, no evidence of a disease process in humans similar to distemper in canines has emerged; distemper is nearly always fatal in canines; and measles virus is known to infect the brain in human only rarely. Those diseases are discussed below.

The measles virus is a widely-recognized cause of several types of brain diseases, specifically, post-measles infectious encephalomyelitis ["PIEM"],[335] measles inclusion body encephalitis ["MIBE"], and SSPE. The latter two conditions are considered to be persistent measles viral infections because they occur months or years after measles disease as the result of ineffective clearance of the measles virus from the body. Measles vaccine virus may cause or contribute to fatal respiratory or neurological disease in severely immunocompromised recipients. In these rare cases, characteristic tissue damage (inclusion bodies or giant cells) are observed. Cedillo Res. Ex. V at 10-11.

a. Post-measles viral encephalomyelitis (PIEM).

This condition is presumed to be an autoimmune disease. It occurs in individuals after infection with measles, mumps, rubella, vaccinia, varicella, or influenza viruses. When it occurs after measles infection, it appears primarily in those who contracted the disease later in childhood, between five to ten years of age. Cedillo Tr.

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[334] In rare complications of measles discussed below, the virus spreads to the brain, causing death in most cases. These deaths, however, occur months or years after the measles infection. Doctor Kennedy also acknowledged that persistent morbilliviruses generally result in death to the host and canine distemper virus causes death in most canines infected. Cedillo Tr. at 789-91.

[335] This condition is sometimes called post-measles viral encephalomyelitis, infectious encephalitis, or acute disseminated encephalomyelitis ["ADEM" or "ADE"].

at 1626, 2743A-44. It is a monophasic illness[336] that presents with focal neurologic deficits, motor or sensory problems, impairment of consciousness, and seizures. Onset generally occurs within days to a few weeks after the measles infection. Perivascular inflammation and demyelination are common findings. Cedillo Tr. at 1626; Snyder Tr. at 836A-37A; E. Norrby and K. Kristensson*, Measles Virus in the Brain*. BRAIN RES. BULL. 44(3): 213-20 (1997), filed as Cedillo Res. Ex. DD, Tab 8 ["Norrby and Kristensson"].

The condition is considered autoimmune because no evidence of measles virus has been detected in the brains of those affected. The general opinion of virologists is that this condition is due to an autoimmune reaction that manifests as encephalitis. Snyder Tr. at 836A-37A.

b. Persistent Measles Virus Infections.

(1) Viral Persistence in General.

In an introduction to a medical journal article,[337] read repeatedly into the record in *Cedillo*, Dr. Michael Oldstone, one of the world's most highly regarded virologists (*see generally*, Dr. Ward's testimony, Snyder Tr. at 952A-62A), wrote that viruses persist when the host fails to form an appropriate immune response or fails to clear the virus; that viruses can acquire unique strategies of replication by regulating gene expression to persist without killing host cells; and that the diseases caused by replicating viruses are often new and unexpected. The implication drawn from Dr. Oldstone's general statements was that the measles virus could similarly surprise the scientists who study it by persisting in vaccinated children and causing autism.

In the *Snyder* hearing, Dr. Oldstone responded to the use of his statements in *Cedillo* with a letter filed as Snyder Res. Ex. AA.[338] Doctor Oldstone wrote:

> I recently became aware that my work in the field of viral persistence is being quoted in support of the hypothesis that the measles virus component of the [MMR] vaccine is supposedly associated with the development of [ASD].

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[336] As Dr. Wiznitzer explained, "monophasic" means that the victim either recovers from it or dies. It does not recur. Cedillo Tr. at 1626.

[337] M. Oldstone, *Viral persistence: Parameters, mechanisms, and future predictions*, VIROLOGY 344: 111-18 (2006) ["Oldstone"], filed as Cedillo Pet. Ex. 61, Tab VV, at 111.

[338] Petitioners objected to the admission of the second paragraph of this letter (Snyder Res. Ex. AA) as an untimely filed expert report on the ultimate issue in this case. Snyder Tr. at 11-12. At the hearing, I indicated that the parties could address this issue in their post-hearing briefs. However, I also indicated that, to the extent that Dr. Oldstone was stating that his work did not support the proposition for which it was repeatedly cited, I would consider the entire letter as rebuttal evidence. Snyder Tr. at 15-16. I did not consider Dr. Oldstone's opinion as substantive evidence in forming my opinion on causation.

> Measles virus has been a focus of my laboratory for many years so this autism/measles link has been of interest to me. Further, I should state up front that I see at present no evidence whatsoever for such a link.

Even without considering Dr. Oldstone's letter, the general statements in Dr. Oldstone's 2006 article (Cedillo Pet. Ex. 61, Tab VV) hardly constitute evidence that the measles virus actually persists to cause autism. Many viruses persist in the body, with or without immune suppression. HIV, hepatitis C virus and the herpes viruses are all examples of viruses that commonly persist in immunologically normal individuals. Cedillo Tr. at 2820-22. In contrast, measles virus is known to persist only rarely, and when it does so, it is almost invariably fatal. Cedillo Tr. at 1626-27, 2785-87, 2791-92A.

(2) SSPE.

SSPE and MIBE are the two diseases recognized to be associated with persistent measles virus in humans. Of the two, SSPE has been found only after wild-type measles infection. Snyder Tr. at 834A; Cedillo Tr. at 2785. The symptoms of the disease, which is almost universally fatal, appear seven to ten years after the wild-type measles infection.[339] Cedillo Tr. at 2785.

The most common clinical picture for SSPE involves a confusing clinical presentation, beginning at least five to seven years after a wild-type measles infection. Diagnosis is initially difficult, but after progressive deterioration is observed, a diagnosis of SSPE is entertained and confirmed. A deterioration in school performance is sometimes an early symptom; others include attention deficits, problems in concentration, jumps and jerks (called myoclonus), and other movement disorders. Both a characteristic EEG abnormality and high levels of antibody to measles are found in the CSF of individuals with SSPE. Brain imaging studies show big ventricles, which are indicative of a shrinking brain. By the time the first symptoms are present, the disease is already widespread throughout the nervous system. Snyder Tr. at 842A-43A, 941A; Cedillo Tr. at 1627-28, 2785-89.

The disease is rare, only occurring in around 1 in 1,000,000 children,[340] and primarily in those who were less than two years of age when they contracted measles. The pathogenesis of the disease process is not known, but the virus likely enters the brain of the children at the time of the original infection. Because the disease develops in those who had a mild case of measles, it is possible that their bodies did not mount an appropriately strong immune response. The virus replicates slowly, building up to a threshold of infection sufficient to trigger disease symptoms. After lapsing into a coma,

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[339] Doctor Wiznitzer placed the onset as early as three years after exposure to the wild-type virus. Cedillo Tr. at 1627. However, I accept Drs. Griffin and Ward's testimony of a five-to-ten year latency period as correct, based on their greater expertise in measles virology.

[340] *See* Norrby and Kristensson, Cedillo Res. Ex. DD, Tab 8. Doctor Griffin's chapter in FIELDS VIROLOGY, Cedillo Res. Ex. R, Tab 18, at 1417, also places the figure at 1 in 1,000,000.

the children die within a year or two of the onset of neurological symptoms. Cedillo Tr. at 1627-28, 2785-89A; Snyder Tr. at 842A-43A.

Autopsies of SSPE victims find inclusion bodies in the infected cells of the nervous system. Staining for virus antigen demonstrates widespread virus, affecting both neurons and glial cells. The virus does not appear to target selected areas of the brain. Most of the deterioration is caused by neuronal death. Cedillo Tr. at 2789A-90; Snyder Tr. at 842A. In contrast to the extensive inflammation seen in the brains of victims of viral or bacterial encephalitis, there is surprisingly little inflammation in the brains of SSPE victims. Snyder Tr. at 941A-42A.

The epithelial and endothelial cells the measles virus commonly affects will eventually die, whether from programmed cell death or from the virus itself. Eventually, as these cells die and are replaced by other epithelial and endothelial cells not infected with the virus, the virus is cleared from the body and no lasting damage can be observed. However, neuronal cells are not replaced when they die, leading to observable damage in the brains of SSPE victims. Cedillo Tr. at 2827A-28.

The measles virus that persists in the brains of SSPE victims exists in a heavily mutated form. The virus cannot bud. It is able to manufacture the proteins that are formed by the front end of the genome in abundance, but is unable to assemble complete copies of itself. Because these proteins exist, an antibody response can be generated. Most children with SSPE have extremely elevated levels of anti-measles antibodies in their brains and CSF as compared to the levels in their blood. One of the diagnostic criteria for SSPE is a comparison of the ratio of CSF anti-measles antibody to peripheral blood anti-measles antibody. In normal individuals, levels of anti-measles antibodies are higher in the blood than in the CSF, because the immune response to the virus occurs in the blood or lymph nodes. In the case of persistent viral infection of the brain, the CSF levels are higher because the immune response is occurring in the brain. Cedillo Tr. at 1829A-31A.

The B cells in the brains of SSPE patients make an antibody that is measles-specific. They produce the oligoclonal bands measured in CSF that are diagnostic of the disease. Snyder Tr. at 841A. In SSPE, the inflammatory response in the brain includes CD4 and CD8 T cells, monocytes, and B cells. FIELDS' VIROLOGY, Ch. 44, at 1418.[341] There is no solid evidence in SSPE that the virus causes altered cytokine levels. Snyder Tr. at 842A.

(3) MIBE.

Unlike SSPE, MIBE occurs only in individuals, primarily children, with profoundly compromised immune systems, such as those with cancer, congenital immunodeficiency, or HIV, at the time of the measles virus infection. Within months of

[341] Cedillo Res. Ex. R, Tab 18.

the initial infection, they develop symptoms of neurologic deterioration or develop pulmonary disease and giant cell pneumonia. Cedillo Tr. 2790-92. Pathological analysis of brain tissue from MIBE victims showed gliosis with inclusion bodies in glial cells and neurons, but very little inflammation. Norrby and Kristensson, Cedillo Res. Ex. DD, Tab 8, at 214.

MIBE presents with symptoms including altered mental status, seizures, and focal neurologic deficits. Its onset is between one and ten months after the measles infection. It relentlessly progresses to death in nearly all who contract it. Cedillo Tr. 1626-27, 2792.

There are at least two case reports of MIBE following MMR vaccination. In both cases, the child was immunosuppressed at the time of vaccination. In the earliest reported case, occurring 30 years ago, the child died of giant cell pneumonia, but had infection in the brain and in all the tissues examined. The more recent case[342] involved a child with a significant, but unrecognized, immune deficiency at the time of vaccination. The child developed MIBE between eight and nine months after the measles vaccination. Snyder Tr. at 834A-835A; Cedillo Tr. at 1068-69A.

(4) Is Autism Another Persistent Measles Infection?

Doctor Kinsbourne acknowledged that autism does not resemble the recognized two disorders of the brain caused by persistent measles virus. He argued, however, that, simply because there are two known neurologic conditions caused by a virus does not preclude a third neurologic manifestation. He referred to Dr. Dyken's measles-induced neuroautistic encephalopathy ["MINE"] theory, that autism is caused by an atypical response of the brain to the measles vaccine virus. Snyder Tr. at 454A-456A.

Based on a 2004 "editorial"[343] by Dr. Paul Dyken, first provided to the court and respondent on the final day of evidence presented in the *Cedillo* case, yet a third theory of vaccine causation of autism emerged.[344] Doctor Dyken speculated that if the wild-type measles virus could cause SSPE, perhaps the attenuated measles vaccine virus could cause a milder, non-fatal condition, such as autism. He relied heavily on Dr.

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[342] Bitnun, Cedillo Pet. Ex. 61, Tab K.

[343] P. Dyken, *Some aspects about the clinical and pathogenetic characteristics of the presumed persistent measles infections: SSPE and MINE*, J. PEDIATRIC. NEUROL. 2(3): 121-24 (2004) ["Dyken"], filed as Cedillo Pet. Tr. Ex. 17. Although titled an "editorial," the paper recounted Dr. Dyken's examination of some of the U.K. claimants. The paper was received for publication on June 4, 2004, and accepted the following day, indicating that peer review was unlikely. I note that the copy of this article electronically filed by petitioners was missing two pages; however, I have analyzed the entire article, based on the paper copy supplied to me during the *Cedillo* hearing.

[344] Earlier in the *Cedillo* trial, Dr. Kinsbourne presented the inflammation-encephalopathy theory and the over-arousal theory. It was not until the *Snyder* hearing that Dr. Kinsbourne merged the two theories and then mentioned the MINE theory as an alternative.

Wakefield's 1998 report, and the purported findings of measles virus in the tissues of autistic patients, for this hypothesis. Although Dr. Dyken's hypothesis was speculative, and based on no research findings other than Dr. Wakefield's and Dr. Dyken's own evaluation of 12 children involved in the U.K. MMR litigation, he presented his theory as established fact: "Those who develop MINE do not completely neutralize the live-attenuated virus and an aborted form of the virus ensues." Dyken, Cedillo Pet. Tr. Ex. 17 at 123.

Although Cedillo Pet. Tr. Ex. 17 was published in 2004, Dr. Griffin had never heard of MINE nor of Dr. Dyken. In her more than 30 years of studying the measles virus, Dr. Griffin had no reason to link persistent measles virus with autism. Cedillo Tr. at 2854-55. Doctor Ward shared Dr. Griffin's skepticism about this editorial, noting that Dr. Dyken took published articles without critically examining them, and postulated a mechanism by which measles vaccine virus persistence could cause autism. After Dr. Dyken's editorial was published, many of the problems in the studies upon which it was based became known. Doctor Ward found it significant that Dr. Dyken had not published anything new on MINE since 2004. Snyder Tr. at 942A-43A.

G. Finding Measles Virus in Tissue.

1. Introduction.

Without positive test results for measles virus, petitioners cannot establish the logical connection necessary between theory and injury. As Dr. Kinsbourne admitted, the positive test results for measles virus were necessary to establish the logical sequence of cause and effect for vaccine causation.[345] Cedillo Tr. at 1180A-81.

Measles virus was reportedly found in samples taken from claimants in the U.K. litigation and from some of the petitioners in the OAP.[346] Petitioners relied on the positive finding for measles virus in children with autism and gastrointestinal illness, to support their theory that persistent measles virus caused their autism. Much of the evidence introduced in the general causation case, and in Colten's specific case, concerned whether the positive test results for measles virus were sufficiently reliable to be given any weight as evidence.

The testing was performed by Unigenetics, an uncertified laboratory, founded by

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[345] I am mindful of Dr. Corbier's opinion on causation, which also relied heavily on findings of measles virus in affected children. Although he indicated he would find in favor of MMR causation, even without evidence of viral persistence, that portion of his opinion was limited to autoimmune reactions. Part E, above, explains the lack of support for his opinions on impaired immune function and autoimmunity as another causal mechanism.

[346] Positive test results were reported for both Michelle Cedillo and Colten Snyder. I address Colten's specific test results in Section VIII, below. The discussion in this section concerns the reliability and validity of the positive findings for measles virus in general.

Dr. John O'Leary and Dr. Orla Sheils at Trinity College in Dublin, Ireland.[347] Cedillo Tr. at 811A-13; Snyder Tr. at 383A-84A. Information regarding Unigenetics' operations was reported in a paper published by Dr. Uhlmann.[348] A paper by Dr. Kawashima appeared to confirm Unigenetics' findings.[349] Doctors Kennedy and Hepner testified that Unigenetics properly performed the tests for measles virus and that the laboratory's results were reliable.[350]

Respondent mounted an overwhelming challenge to the reliability of Unigenetics' test results for measles virus. Because of petitioners' objections to the use of information derived from the U.K. MMR litigation, I have divided the discussion of respondent's challenges to Unigenetics' results into two parts: (1) evidence available from the public domain, and (2) evidence unsealed from the U.K. litigation. Some background information on molecular biology, the genetic composition of the measles virus, and the laboratory techniques used to test for the presence of measles virus is necessary in order to understand the significance of the problems found in the Unigenetics laboratory.

Much of the background information on molecular biology and PCR testing in this opinion is drawn from the testimony of one of petitioners' witnesses, Dr. Karin Hepner. Additional information was supplied by Drs. Kennedy, Ward, Rima, Bustin, and

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[347] A reference or certified laboratory is required to undergo external evaluation to determine how well it performs. Samples, known to be positive or negative, are sent from a certifying agency, with the results reported from those samples used to evaluate the laboratory's procedures. Unigenetics was never a reference laboratory. Cedillo Tr. at 2034; Snyder Tr. at 989A-90A. Doctor Kennedy also testified that Unigenetics laboratory is no longer operating. Snyder Tr. at 400A.

[348] V. Uhlmann, *et al.*, *Potential viral pathogenic mechanism for new variant inflammatory bowel disease*. J. CLIN. PATHOL: MOL. PATHOL. 55: 84-90 (2002) ["Uhlmann"], filed as Cedillo Pet. Ex. 61, Tab GGGG. Doctor Uhlmann was a post-doctoral fellow in Professor O'Leary's laboratory at the Coombe Hospital, Dublin, Ireland. The methodology described in the Uhlmann paper was the O'Leary laboratory's. Cedillo Tr. at 1938A. Doctor Wakefield was listed as a co-author on the Uhlmann paper, as were Drs. Orla Sheils and John O'Leary.

[349] H. Kawashima, *et al., Detection and Sequencing of Measles Virus from Peripheral Mononuclear Cells from Patients with Inflammatory Bowel Disease and Autism,* DIG. DIS. SCI. 45: 723-29 (2000) ["Kawashima"], filed as Cedillo Res. Ex. T, Tab 18. Doctor Wakefield was listed as a co-author on this study.

[350] Doctor Kennedy also testified about unpublished data concerning immunohistochemical tests for measles virus protein performed by Unigenetics laboratory. Snyder Tr. at 329A-30A. He referred to a meeting he attended with Dr. Sheils at which immunohistochemical testing was discussed. Cedillo Tr. at 744-46. Doctor Chadwick testified about immunohistochemical testing at the Royal Free Hospital. Cedillo Tr. at 2283-89A. In view of the subsequent failure to publish any results of the immunohistochemical testing, Dr. Chadwick's testimony that the immunohistochemical results from the Royal Free Hospital could not be reliably reproduced, and other evidence that Unigenetics did not perform immunohistochemical testing (*see* Cedillo Tr. at 651-52A), I have given Dr. Kennedy's testimony on the positive results of these tests little weight.

Chadwick. There were no genuine issues of material fact in Subsections 2-4, below.[351] The matter in controversy is the reliability of results reported from testing at the Unigenetics laboratory, the discussion of which is contained in subsection 5.

2. A Molecular Biology Primer.

Deoxyribonucleic acid ["DNA"] is made up of four types of nucleotides (sometimes called "bases"), adenine ["A"], guanine ["G"], thymine ["T"], and cytosine ["C"]. These nucleotides form bonds: T binds only to A; G binds only to C, creating what are called "base pairs." DNA molecules resemble a very twisted spiral staircase, with the base pairs forming the rungs. One rung could be formed by the T nucleotide on one side and the A nucleotide on the other; a second rung might be identical to or the mirror image of the first, or it might be composed of a G-C bond.

The nucleotides are bonded in two chains forming the sides of the ladder, as well as bonded to their paired base on the opposite chain. When the bonds between the base pairs are "unzipped" or broken, as if cleaving a ladder from top to bottom, each strand of the molecule forms a mirror image of the other. Splitting the molecule in this manner, in the body or in a test tube, is the first step in replicating, or amplifying, DNA. The splitting of the rungs is accomplished by introducing helicase, a naturally occurring enzyme, or by heating (denaturing) the DNA. Cedillo Tr. at 589A-92A.

After splitting, the missing half of the rungs on each side of the ladder are replaced by a polymerase enzyme, which adds the missing nucleotides to recreate the complementary strand of DNA. Two identical copies of the original DNA sequence are created. Cedillo Tr. at 593A-97A.

The sequence of A, G, T, and C nucleotides forms unique patterns of "words," formed from the four "letters." Sequencing involves ascertaining the nucleotide order in a particular DNA segment. DNA segments form genes. DNA databanks contain the exact order of nucleotides for many genes. If a scientist finds a particular DNA sequence and wants to determine the source of the DNA, a databank inquiry can be made. Determining the nucleotide sequence requires, as a first step, that the strand of DNA containing those nucleotides be "amplified" or copied. Cedillo Tr. at 589A.

If the target strand contains RNA instead of DNA, the RNA must first be converted to DNA, because RNA cannot be amplified by PCR. In RNA, one of the bases that makes up the molecule is different from the four bases found in DNA. In the process of making the RNA into DNA, the corresponding DNA base is substituted. If the RNA is negative sense, an additional step is necessary. The negative sense RNA must be converted to positive sense RNA, and then converted to DNA. The process of

[351] Doctor Ward commented that Dr. Hepner did a very good job of explaining PCR testing. His only issue with her testimony was that she left the impression that PCR is simply a matter of putting a sample in a machine, pressing a button, and getting correct results at the other end, ignoring the need for subjective interpretation or considering the possibility of human or machine errors. Cedillo Tr. at 1840A.

turning RNA into DNA is called “reverse transcription” [“RT”]. The DNA that is created is called “cDNA,” reflecting that it is a copy of the RNA. Cedillo Tr. at 603A-04A; Cedillo Pet. Ex. 120 at 9.

The conversion of RNA to DNA uses an enzyme called reverse transcriptase and a primer composed of T bases to create a complementary version of the RNA. The original RNA is displaced, and bases bind to the complementary version, producing double stranded cDNA. Cedillo Tr. at 604A-05A.

3. Polymerase Chain Reaction.

Polymerase chain reaction is a method of exponentially replicating a strand of DNA. Cedillo Tr. at 592. Using conventional (or solution-based) PCR, extremely small quantities of DNA can be amplified, creating enough DNA to produce a visible “band” on a gel. Any specific section of a DNA strand can be targeted for amplification, so long as at least some part of the sequence is known. Cedillo Pet. Ex. 120 at 9.

Although extensively automated, subjective assessments are required in PCR analysis and, therefore, both mechanical and human errors are possible. Given the subjective assessments required, reports of results can be manipulated. Cedillo Tr. at 1840A-43A. For these reasons, it is essential to establish strict standard testing protocols and quality control measures.

a. Steps in Conventional PCR.

(1) Selecting Primers.

The first step in amplifying DNA is to select primers. A “primer” is a section of DNA that is complementary[352] to a portion of the target strand of DNA. A primer consists of a nucleotide sequence of about 20 nucleotides. Primers are designed to be specific to the two ends of the target sequence. They can be purchased commercially, and are selected based on the sequence of nucleotides in the target section of the gene. Cedillo Tr. at 594-96A.

The primers need to be specific to the target DNA to be amplified and the specific section of DNA to be amplified should not be present in any other gene. If the primers are not specific enough, DNA other than the target sequence might be amplified along with (or instead of) the target DNA, amplifying the wrong substance, resulting in a false positive. Cedillo Tr. at 596A-97A, 1983A-84A.

[352] “Complementary” means that if a T nucleotide is the first base on the target DNA, the first base on the primer would be the T nucleotide’s complement, the A nucleotide. Doctor Hepner called this a “mirror image.” Cedillo Pet. Ex. 120 at 9.

When designing an assay,[353] sequencing the amplified DNA [the "amplicon"] to be generated, and then comparing the sequence to a known sample of the target substance, is the best method for determining if the primers in the assay are sensitive enough. If the laboratory does not sequence the target when designing, validating, and optimizing the assay, the laboratory cannot be certain it is testing exclusively for the target substance. Cedillo Tr. at 1945A.

(2) Amplification.

After selection of the appropriate DNA primers, the target DNA is denatured (split by heating). A polymerase is added, and two strands of DNA are then formed from the original strand. This is one cycle in PCR. A second cycle increases the two strands to four by heating the DNA to induce splitting, and reforming each of the split strands by the added polymerase. A third cycle turns the four strands into eight, and the process proceeds exponentially, normally through 20 to 40 cycles, in conventional, solution-based PCR. Amplification is followed by running the amplicon in gels and comparing the bands. Cedillo Tr. at 1941-42A. PCR can produce billions of copies from one strand of DNA. Cedillo Tr. at 598A-99A.

(3) Melt Curves.

PCR machines can generate a "melt curve," which is the temperature at which the two strands of DNA that have been amplified will break apart. Each segment of DNA has a specific temperature at which it will break apart, providing a good indication that the sequence being amplified is the sequence sought. If the unknown and known samples have similar melt curves, this is an indication that they are likely to be the same DNA sequence. Cedillo Res. Tr. Ex. 12, slide 15, is an example of a melt curve. A melt curve should be confirmed with gel detection, which compares the size of the DNA molecule amplified with the size of the targeted sequence. Cedillo Tr. at 1844-45.

(4) Gel Detection.

The DNA produced through PCR amplification is placed in wells at one end of an agarose gel. Cedillo Tr. at 1976A-78A. An electrical current is applied to the gel, which causes the negatively- charged DNA to move through the gel in lanes. DNA pieces move through the gel at different rates, depending on their size, with the smaller pieces moving faster. A stain is added to the gel, and under ultraviolet light the pieces of DNA fluoresce, making them visible. Cedillo Tr. at 600-01A. The result of this process is something that looks like a bar code.

The agarose gel contains a DNA standard "ruler" indicating how many base pairs of DNA will reach a particular point in the gel as a result of the electrical current and their size. Since the approximate size (number of base pairs) of the DNA target piece is

[353] In PCR, an assay is the testing process. DORLAND'S at 166.

known, the first step in determining if the primers are specific to the target selected is to compare the bands in the gel to the ruler. If the product is the correct size, the primers likely selected the correct target. Cedillo Tr. at 601A.

b. Real Time PCR.

Real time PCR is a technique for amplifying and detecting DNA in "real time." Real time PCR permits detection of the target sequence as the sample is being amplified, without waiting for the amplified product to be run on a gel and permits quanitification of the amount of the target substance present. *See generally*, T. Nolan, *et. al.*, *Quantification of mRNA using real-time RT-PCR*, NATURE PROTOCOLS, 1(3): 1559-82 (2006) ["Nolan"], filed as Cedillo Res. Ex. UU, Tab 7.

In real time TaqMan PCR (the type of testing performed at Unigenetics), as in conventional PCR, two primers are used, both designed specifically for the targeted gene. However, TaqMan PCR also uses a probe that is complementary to one of the strands of target DNA. Probes are treated to be chemically luminescent. If the target DNA is present, the probe will bind to it, and luminescence signals that the amplification process is working. The fluorescent signal provides an additional level of confidence in the result of PCR amplification, because both the primer and probe sequences must match the target DNA strand in order for the probe to fluoresce. Cedillo Tr. at 609A; Nolan, Cedillo Res. Ex. UU, Tab 7.

The threshold cycle ["CT"] is the first cycle of amplification in which enough DNA is present to detect the fluorescence. The more target DNA available initially, the fewer the number of cycles necessary before a machine can detect the fluorescence. Cedillo Tr. at 612A. By convention, no more than 40-45 PCR cycles should be run on any sample. Cedillo Tr. at 2000-02, 2039. In general, results at 35 cycles or below are acceptable. Results above 35 cycles can be a cause for concern. Cedillo Tr. at 2044.

The results of TaqMan PCR are more reliable than conventional, solution-based PCR because of the additional confirmation from the probe, but TaqMan results are not definitive. The probe may be detecting contamination, or the fluorescence may be an artifact. Any problems with the actual assay itself remain. Sequencing the results is the only method which can determine precisely what was amplified. Cedillo Tr. at 1942A-45A.

TaqMan PCR also permits a determination of the approximate amount of the target DNA sequence in the unknown samples, based on the development of a standard curve. A standard curve is derived by taking a very clean sample of a known quantity of the targeted genetic sequence and diluting it at various concentrations. PCR amplification is then performed. A curve, based on the results from various dilutions and the number of PCR cycles required to produce a signal, is generated. The range of the standard curve must be sufficiently broad so as to include all possible concentrations that might be found in the unknown samples. By comparing the results of an unknown sample against the standard curve, the laboratory can determine how

much of the targeted genetic sequence was present initially. Page 10 of Cedillo Res. Tr. Ex. 13 reflects a standard curve for a gene at various dilutions at factors of 10. When plotted against a standard curve, the unknown samples should be within the ranges established by the standard curve. This range is illustrated in this exhibit by the black dots. Cedillo Tr. at 1987A-89A.

c. Confirmatory Testing.

PCR amplification of a genetic sequence of base pairs does not produce a result that can be directly visualized. The product cannot be examined microscopically and then visually compared to a known sample. Comparing the bands on a gel with the standard ruler in conventional PCR merely tells the investigator whether the amplification produced a molecule of the expected size. To illustrate, a person can determine by touch that a small grapefruit on the table is similar in size, shape, and texture to another fruit inside a paper bag, but cannot definitively state whether the fruit in the bag is a large orange or a small grapefruit. Further examination is necessary to make this determination.

(1) Southern Blot.

In the Southern blot confirmatory test, the gel that produced the bar code results is heated to denature the DNA again, separating the strands. The DNA is removed from the gel and placed in a filter. Additional DNA, treated with either a radioactive or colorimetric label, is added to the filter. The additional DNA added is designed to be complementary to the target gene. If it encounters the target gene and binds to it, a signal is produced, indicating that the target is present. If the target gene is not present, no binding occurs and no signal is produced. Cedillo Tr. at 606A-07A.

To continue the grapefruit analogy, confirmatory testing, such as the Southern blot, permits the investigator examining the object in the paper bag to determine that the object is a citrus fruit, but he is still unable to determine whether it is a large orange or a grapefruit.

(2) Gene Sequencing.

Sequencing the DNA produced by the amplification process is the gold standard in PCR testing, whether using conventional PCR or real time PCR. Cedillo Tr. at 673. Sequencing is the only method that can establish the identity of the amplified sample as the actual target, but the process of sequencing is time consuming. Cedillo Tr. at 824-25, 1941-42B. Sequencing is the equivalent of opening the bag and slicing open the fruit inside to determine if it is a grapefruit.

d. Common Problems in PCR Testing.

Polymerase chain reaction testing has vulnerabilities. Doctor Ward identified some common problem areas: (1) the quality of the RNA tested; (2) contamination of

the laboratory with the massive amounts of DNA produced during the chain reaction; (3) the specificity of the primers and probes used; (4) the use of controls and standards to confirm results; and (5) the subjectivity of some steps of the analysis. Cedillo Tr. at 1840-43; Cedillo Res. Tr. Ex. 12 at 15. Doctor Bustin identified similar areas of vulnerability, both in his affidavit and in his testimony. Doctors Kennedy and Hepner agreed that PCR results can be affected by changes in the study design, variations in the PCR machinery, the specificity and sensitivity of the primers, and by the use of unblinded samples. Cedillo Tr. at 668-70, 818-24A

(1) Quality of RNA Samples.

The quality of the RNA sample is critical to the validity of the test results. RNA is extremely fragile and easily degraded. Cedillo Tr. at 1841A. Tissue samples may be fresh-frozen or formalin-fixed. A fresh-frozen sample is one that is placed in liquid nitrogen immediately upon biopsy. Ordinarily, the quality of RNA obtained from fresh-frozen samples is very good, if handled carefully. If the quantity of the target is low in the sample tissue, fresh-frozen samples offer the best possibility of detecting it. Cedillo Tr. at 1946-47A.

However, research is often conducted on archived materials, samples stored for years after the tissue was formalin-fixed and paraffin embedded. This process degrades RNA, making it less available for reverse transcription. Because the quality of RNA varies so widely, depending on the type of sample from which it is extracted, the results from fresh-frozen and formalin-fixed samples should not be compared. Cedillo Tr. at 1946-47A.

(2) Contamination.

DNA contamination is the “Achilles’ heel” of PCR testing. Contamination is frequent even in the most compulsively monitored laboratories. An open tube of DNA can contaminate an entire lab. If PCR is performed on one DNA molecule, after 38-40 cycles, there would be 2.7 trillion copies of that molecule. If there were 1000 pieces of the DNA initially present, the numbers would be even more massive, astronomically increasing the potential for contamination. Laboratories performing PCR must have procedures to anticipate, detect, and counter contamination. Such procedures can include performing amplifications in rooms separate from the testing location, and in using enzymes to degrade DNA. Cedillo Tr. at 1841A-42. Additionally, laboratories must test for contamination by using environmental controls, no-template (negative) controls,[354] and, when RNA is the source material, by omitting the reverse transcription step. If the reverse transcription step is omitted, any DNA produced is the result of

[354] The term “template” refers to the target of the analysis, which would be the measles virus gene sequences. Cedillo Tr. at 1939A-40. A no-template control would be one which, by design, contained none of the target gene.

contamination. Cedillo Tr. at 1975A-76A, 1980A-83A.

(3) Specificity of Primers.

The primers used must be absolutely specific for (identical to) the target to be amplified. If they are not, massive amounts of misinformation will be generated because the primers delineate the target for amplification. Cedillo Tr. at 1983A-84A. Primers should not be too similar to one another. If the two primers are of similar length, they may bind and stick together, resulting in amplification of the primers, rather than of the target. Cedillo Tr. at 1984A.

(4) Controls and Standards.

It is essential to standardize laboratory procedures. A laboratory's standard operating procedure ["SOP"] functions as a recipe, allowing an investigator to repeat results over time, demonstrating reliability. For example, an SOP should specify how samples are to be obtained, how RNA is extracted and assessed for quality, and the temperature and time used in the denaturing process. Cedillo Tr. at 1969A-70. Time and temperature are both crucial in PCR. Once the primers are developed, and the optimum temperature for the assay is established, it is important to continue to use that temperature and timing to ensure consistent results. Cedillo Tr. at 1977A-77B.

Once parameters are set on the machine used for analysis, the parameters should be locked. Minor changes in machine parameters can alter results from positive to negative (or vice versa). Cedillo Tr. at 1843A-44.

Positive controls are also essential in PCR testing. A positive control is a sample containing the target DNA, such as cells grown in culture containing the virus, or other tissue known to contain the virus, such as brain tissue from an SSPE victim. Positive controls verify whether the assays used are working properly. The positive control must always test positive for the presence of the virus. If it does not, there is a problem with the assay used to detect the virus. Laboratories should use positive controls on every run to assess how efficiently their assays are working. Cedillo Tr. at 1938A-39A.

Likewise, a negative (no-template) control is crucial to an assessment of whether the analysis of unknown samples is working properly. A negative control is a sample known to contain none of the substance for which the unknown samples are being tested. If a negative control sample tests positive, there is a problem with the assay. Cedillo Tr. at 1939A.

Although testing for false positives and adequate internal consistency controls are essential to obtain reliable and scientifically valid results from PCR testing, the only method that can confirm the results is sequencing the DNA generated. Cedillo Tr. at 1842- 43A.

(5) Blinded Testing.

Interpretation of banding and other aspects of the PCR process are subjective. Blinded testing means that the person determining if the test results are positive or negative is unaware of the source of the sample or the results desired. Blinding the interpreter avoids the possibility of biased observations. Cedillo Tr. at 669-70, 2863.

4. Issues in Measles Virus PCR Testing.

Doctor Rima began working with PCR shortly after the technique was invented. He explained that it is an extremely powerful tool, but some of the drawbacks were not initially recognized. It works very easily with DNA molecules, but it is less sensitive with RNA molecules because of the need for reverse transcription. In addition, the plasmids used to make the standards for PCR testing provide a source for contamination of the samples. Snyder Tr. at 851A-53A.

Because the measles virus is a negative sense RNA virus, the additional steps of converting the RNA to positive sense RNA, and then to DNA, introduce additional opportunities for errors in the process. If DNA is detected in the RNA sample prior to this conversion process, the DNA detected is a contaminant. Cedillo Tr. at 603A-04A, 1975A-76A.

When replicating, the measles virus produces genes in a particular order, creating many more copies of the genes first in the genetic sequence than those later in the sequence. Cedillo Tr. at 729A-33; Snyder Tr. at 917. In order, the genes are called N, P/V/C, M, F, H, and L. Cedillo Pet. Tr. Ex. 7 at 7. In the process of replicating, the virus transcribes the front end of its genome more frequently than the back end, making more copies of the N gene, the first gene present in the viral RNA, than of the F or H genes. Cedillo Pet. Tr. Ex. 8 at 15.

If the F gene is reliably detected through PCR, the N gene and all the genes in between were produced. However, it makes more sense to search for the N gene rather than the F gene, because there will be more copies of the N gene, providing the best opportunity for detecting the presence of a measles gene in a sample. Snyder Tr. at 917-919.

5. The Unigenetics Laboratory.

The Unigenetics laboratory had several of the hallmarks of unreliability noted in *Daubert.* It was established, primarily, if not solely, for the purpose of supporting the claimants in the U.K. MMR litigation.[355] Its results were not reproducible by

[355] Doctor Rima testified that Unigenetics' only commercial activity was testing samples provided by litigants in the U.K. MMR litigation. Snyder Tr. at 927A-29. Based on the positive results filed as evidence for both Michelle Cedillo and Colten Snyder, the laboratory also tested samples submitted by litigants in the OAP.

independent investigators, and its quality control problems were so pervasive that they suggested gross negligence, if not outright scientific fraud.

There were several sources of information about operations in the Unigenetics lab. The Uhlmann paper, Cedillo Pet. Ex. 61, Tab GGGG, described testing methods and results from the Unigenetics lab. Doctor Kennedy testified about his meetings with Dr. Sheils, one of the lab's directors, where the laboratory's testing practices and methods were discussed. Doctor Hepner testified about her review of the Uhlmann paper and her conclusions about the reliability of Unigenetics' results. Several of respondent's witnesses criticized the Uhlmann paper, based on their own research as well as on the findings of other researchers. Doctor Bustin testified about two visits he made to the laboratory as part of the U.K. MMR litigation, his examination of laboratory notebooks, and the test runs he conducted on Unigenetics' PCR machines. Doctor Rima described problems he found with Unigenetics based on his own role in the U.K. MMR litigation. Both Drs. Rima and Bustin also provided testimony that was not derived from knowledge obtained in the U.K. MMR litigation.

Because of the motions to strike the evidence derived from the U.K. litigation filed by the petitioners in *Cedillo* and *Hazlehurst*, based on their inability to obtain the data underlying Drs. Bustin's and Rima's testimony and reports and Dr. Simmonds' report, I have separated my analysis of the evidence concerning the reliability of Unigenetics, based upon the source of the evidence. Criticisms of the laboratory results, based on the Uhlmann paper and other matters in the public domain, are treated separately from criticisms of the laboratory based on matters derived from the U.K. litigation. My legal conclusion, set forth in Section I, Part E, above, is that petitioners waived any objection to the use of information obtained from the U.K. litigation by their failure to file a request to unseal the underlying data and additional expert reports. However, an analysis of the public evidence alone clearly demonstrates that the results from Unigenetics cannot be relied upon as evidence of the persistence of measles virus in children with autism. When considering the U.K. litigation information, the evidence that Unigenetics' results are not reliable is overwhelming. Unigenetics' operations reflect unsound applications of the sound scientific process of PCR testing.

a. The Uhlmann Paper.

The Uhlmann paper began by recapping Dr. Wakefield's findings of ILNH in children with autism and his hypothesis that the ILNH represented the persistence of a viral antigen at sites of ILNH. The authors noted that "preliminary" immunohistochemical data suggested that the measles virus was present in the lymphoid tissue.[356] The paper described the molecular biologic techniques used to

[356] The reference in the paper to immunohistochemistry is somewhat ambiguous regarding when and where the immunohistochemistry was done. The Unigenetics lab, which provided the data from which the Uhlmann paper was drawn, did not use immunocytochemistry or immunohistochemistry. Cedillo Tr. at 650-52A; Snyder Tr. at 848A-49A, 914A-16A. If the paper's reference was to previous

detect and measure measles virus in the terminal ileum of children with ILNH and developmental disorders.[357]

Biopsies from 91 case children and 70 developmentally normal controls were tested and compared. Positive controls for measles virus RNA included tissue from two cases of SSPE and from measles virus-infected Vero cells. Both fresh-frozen biopsies and formalin-fixed paraffin tissue blocks were used as sources of RNA.

The paper covered the steps used in testing the RNA by TaqMan PCR. Primers and probes were designed for regions of the measles virus N, H, and F genes; Southern blot analysis was used to confirm specificity of the probes; PCR was performed using the TaqMan reverse transcription reagents with appropriate controls, including no-template and no amplification controls; and quantitative measurements were made using standard curves. In situ PCR was also performed.[358]

The authors reported that 75 of the 91 case children had measles virus in their ileal lymphoid tissue, compared to only five of the control children. TaqMan PCR testing found positive results for measles virus in 70 of the 91 case children tested, albeit at low copy numbers in most cases. Only four of the 70 control children tested positive for measles virus, with all of the positive findings coming from control samples obtained during appendectomies. No measles virus was detected in normal children or children with isolated ILNH.

In situ PCR testing found that 42 of 57 tissue biopsies were positive for the N gene; four samples were inconclusive, and 11 were negative. One of the five control children with normal bowel mucosa had detectable N gene RNA present. The virus was found in DC and some lymphocytes.

In comparing TaqMan and in situ PCR testing, the researchers obtained some

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immunohistochemical testing of samples at the Royal Free Hospital, Dr. Chadwick's testimony indicated that this testing could not be replicated by other researchers. Cedillo Tr. at 2288-89A. *See also* Iizuka, Cedillo Res. Ex. BB, Tab 46 (finding that the measles-related antigen found in the intestine of Crohn's disease patients by Dr. Wakefield was derived from human protein, not measles virus). The witnesses used the terms "immunohistochemistry" and "immunocytochemistry" in referring to the same method of testing for viruses. The terms are interchangeable. Snyder Tr. at 935A.

[357] The Uhlmann paper described the use of several techniques for testing samples for the presence of measles virus: (1) solution-based RT PCR, which Dr. Rima characterized as a standard technology; (2) in situ RT PCR, which he characterized as an experimental technology that was not properly developed; and (3) TaqMan PCR. Cedillo Tr. at 613A-14, 650-52A; Snyder Tr. at 848A-49A, 914A-16A.

[358] The Uhlmann study also involved the collection of gastrointestinal tissue by biopsy and the amplification of DNA directly in the tissue, rather than extracting the DNA from the tissue and conducting the amplification in a test tube. This is known as "in situ" PCR. Cedillo Tr. at 613A-16A.

discordant results.[359] Although 56 biopsies were examined using both techniques, the authors reported that concordant results were obtained in 42 samples (37 positive in both and five negative in both). They reported discordant results in eleven cases, but the paper did not explain why some of the results discussed totaled only 53, when 56 biopsies were examined with both techniques.

The authors concluded that their data confirmed an association between the presence of measles virus and gut pathology in children with developmental disorders.

b. Doctor Hepner's Analysis of the Uhlmann Paper.

Doctor Hepner testified that, based on the Uhlmann paper, the Unigenetics laboratory used appropriate PCR techniques, properly performed PCR amplification of the extracted RNA, used appropriate positive and negative controls, and, therefore, obtained reliable results. Cedillo Tr. at 616A-23A. Based on the high copy numbers of measles virus RNA found in some of the samples, she concluded that the positive findings were not artifacts and represented actual virus detection. Cedillo Tr. at 642. Doctor Kennedy testified that, at least with the high copy number results, he considered the Unigenetics' results to be reliable. Snyder Tr. at 345-46A, 385A.

Unigenetics' use of known positive and negative samples provided one level of control. As Dr. Hepner explained the concept, if a negative control tested positive, there was either a flaw in the experimental design or contamination. A flaw in the experimental design might result from using primers that were not specific to the target. Cedillo Tr. at 618A-19A.

A second level of control involved the use of experimental controls. In the Uhlmann study, the experimental group consisted of ASD patients with idiopathic bowel disease. The control group involved developmentally normal children. Both groups had biopsies of gastrointestinal tissue tested by Unigenetics. According to Dr. Hepner, the standard laboratory practice should involve the simultaneous testing of samples of the control group and the experimental group. Cedillo Tr. at 619A-21A.

Doctor Hepner discussed the Uhlmann paper[360] in some detail. Based on the paper, she asserted that, in their conventional PCR testing, the laboratory's positive

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[359] "Discordant results" refers to a single sample testing both positive and negative for the measles virus, on different runs using the same primer, or on runs using different primers. Primers are specific to the gene being sought. A sample that tests positive for one measles gene, but negative for another, should not be reported as positive for the presence of measles virus. Cedillo Tr. at 672. If one gene test is positive, but the other is negative, the likelihood that the virus was actually present is considerably more doubtful. Cedillo Tr. at 1961A-62A.

[360] During Dr. Hepner's testimony, the Uhlmann paper was identified as Cedillo Pet. Ex. 63, Tab U. It was also filed as Cedillo Pet. Ex. 61, Tab GGGG. The Uhlmann paper was referenced by several of the experts, and, thus, it was filed as an attachment to each report. For consistency, I use the Cedillo Pet. Ex. 61, Tab GGGG, designation.

control was consistently positive and the "no-template" control was consistently negative. The varied results for presence of the virus, and the different copy numbers obtained, indicated that the experimental design was appropriate and working properly. Cedillo Tr. at 622A-23A. Confirmatory testing by Southern blot gave her confidence that the targeted gene was being amplified because the Southern blot produced a molecule of the predicted size. Cedillo Tr. at 624A.

She used Figure 2 (A) of the Uhlmann paper, which showed the bands produced by gel electrophoresis, to demonstrate that the positive results for measles virus were reliable. The first seven lanes of the gel (lanes 1-7) in Figure 2 (A) involved primers testing for the measles virus F gene. The next seven lanes (lanes 8-14) reflected tests for the measles virus H gene. According to Dr. Hepner, testing for two genes, both with positive results, enhanced the reliability of the positive test results for measles virus

Lanes 1 and 2 represented positive controls, one from measles infected-Vero cells and one from the brain tissue of an SSPE victim. Lanes 3-6 were from children with ASD. Lanes 7 and 14 represented no-template controls, both of which appropriately tested negative. Other than the use of a primer to select the measles virus H gene as the target for amplification, the samples in Lanes 8-14 were identical to those in Lanes 1-7.[361] Cedillo Tr. at 624A-26A.

Doctor Hepner's conclusion was that the results from the Uhlmann study were valid (Cedillo Tr. at 626A), but she acknowledged that other labs were unable to reproduce Dr. Uhlmann's findings. Cedillo Tr. at 628.

c. The Kawashima Paper.[362]

This study reported the detection of measles virus genomic RNA by a Japanese laboratory in peripheral blood mononuclear cells ["PBMC"][363] of eight patients with Crohn's disease, three with ulcerative colitis, and nine children with autistic enterocolitis.[364] Controls involved healthy children and patients with SSPE, lupus, and

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[361] It is noteworthy that lanes 1-2 and 8-9 in Figure 2(A), which contain the known positive samples, presented with bright, clear bands, whereas the four ASD children's samples (lanes 3-6 and 10-13) demonstrated fuzzy or nearly nonexistent bands at the appropriate molecular weight for the measles virus gene targeted.

[362] H. Kawashima, Cedillo Res. Ex. T, Tab 18.

[363] PBMCs are the lymphocytes, macrophages, and dendritic cells that remain in blood after the removal of red blood cells, platelets, and neutrophils from peripheral blood. Measles virus (wild-type and vaccine strain) can infect all types of the PBMCs *in vitro*, and presumably *in vivo* as well. Cedillo Tr. at 1848.

[364] The Kawashima study was performed in Japan, but all of the case children (those with autistic enterocolitis) were from the U.K., presumably from samples provided by Dr. Wakefield. Kawashima, Cedillo Res. Ex. T, Tab 18, at 726. Doctor Chadwick's declaration indicated that Dr. Wakefield had invited

HIV. After PCR testing, the gene products were sequenced for specific regions of the measles virus H and F genes. After sequencing, results were reported as consistent with measles virus in one of the Crohn's disease patients (wild-type measles virus), one of the ulcerative colitis patients (vaccine strain measles virus), and three of the children with autism (vaccine strain measles virus). The authors concluded that measles virus persisted in PBMCs in some patients with chronic intestinal inflammation.

The laboratory was unable to find the measles N gene in any of their samples. They speculated that the failure to detect the N gene might have resulted from mutations in the persistent nucleotides. Kawashima, Cedillo Res. Ex. T, Tab 18, at 728.

d. Problems with the Uhlmann and Kawashima Papers.

Criticisms of the Uhlmann and Kawashima papers abound, both in the published literature, and in the testimony and reports in the Theory 1 test cases. The primary criticism involved the inability of other researchers to duplicate their results. Other criticisms included issues concerning the specificity of the primers and probes, the failure to use blinded samples, evidence of contamination, and data omitted from the papers. *See, e.g.,* Cedillo Tr. at 653; 1846-48; Cedillo Res. Ex. QQ at 2-3. Petitioners' experts acknowledged that some criticisms were valid, but contended that the results were, nevertheless, reliable.[365]

(1) Inability to Duplicate Results.

If correct, the results from the Uhlmann and Kawashima papers would work a sea change in measles virology, with significant implications for the diagnosis and possible treatment of both autism and gastrointestinal disease. However, their results contradicted a number of epidemiologic studies that failed to detect any connection between measles virus or measles vaccine and inflammatory bowel disorders or autism. Therefore, it was not surprising that a number of laboratories attempted to duplicate their results. Doctor Ward provided testimony about his own research team's efforts and findings. Additionally, respondent filed a number of articles by Dr. Afzal, a researcher at the U.K. National Institute for Biological Stands and Controls, Division of Virology. Several other witnesses also testified about the lack of scientific reliability of the Uhlmann, Kawashima, and Unigenetics findings.

Dr. Kawashima to give a talk in 1995 or 1996, and thereafter established a link with him. Cedillo Res. Ex. QQ at 2-3.

[365] *See, e.g.*, the testimony of Dr. Hepner, stating that the omission of supporting data in the paper was a valid criticism of Dr. Uhlmann's work. Cedillo Tr. at 653-54.

(a) Doctor Ward's Research Team's Efforts.

Doctor Ward's group initially attempted to duplicate the Uhlmann study, but elected to use PBMCs rather than gut biopsy tissue, based on ethical concerns about performing endoscopies and gut biopsies on autistic children when the tests were not medically necessary.[366] Because the Kawashima paper involved PBMCs and the theory of viral persistence involved transmission through peripheral blood from the gut to the brain, they used PMBCs for their first study.[367] The research team eventually obtained gut tissue from children with autism and gastrointestinal complaints warranting endoscopy, but did not obtain any biopsy samples from autistic children without gastrointestinal complaints. Cedillo Tr. at 1899A-1902A.

Cedillo Res. Ex. BB, Tab 30, is the first of the two D'Souza articles,[368] both of which document the research performed in Dr. Ward's laboratory. In the study documented in the first D'Souza article, researchers collected PBMCs from 54 children with ASD and 34 normal control children. No measles virus was detected by PCR testing in any of the samples. The most significant finding was that, using the Uhlmann primers, PCR testing on the PBMCs was initially positive for the presence of measles virus in both groups. However, sequencing the amplicons demonstrated the amplified material was not measles virus. *Id*. at 1670-71.

Doctor Hepner criticized studies that used PBMCs, rather than gut tissue, to attempt to duplicate the Uhlmann findings, and criticized this D'Souza study for its failure to restrict the study population to children with both ASD and bowel disease. She asserted that the positive results obtained from the Uhlmann primers on the positive control samples demonstrated there was a problem with the study population, not the primers. Cedillo Tr. at 629A-31.

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[366] The autistic children who provided blood samples for this study had a high level of gastrointestinal complaints, as compared to the control children, but the threshold for reporting such complaints included relatively mild symptoms. Cedillo Tr. at 1899A-1902A.

[367] If measles virus persists in children with ASD, it should be present in PBMCs. Both Drs. Kawashima and Bradstreet purportedly found measles virus genomic material in the PBMCs of one of the three children tested. J. Bradstreet, *et al., Detection of Measles Virus Genomic RNA in Cerebrospinal Fluid of Children with Regressive Autism: a Report of Three Cases,* J. AM. PHYSICIANS & SURGEONS 9: 38-45 (2004) ["Bradstreet 2004"], filed as Snyder Pet. Ex. 188. Doctor Kinsbourne testified that if measles virus is replicating in the gut and causing inflammation, immune cells are responding to the inflammation and some will be infected. Immune cells move throughout the body, carrying the replicating virus in their cytoplasm. If measles virus is getting to the brain from the gut, it moves between them via the bloodstream. Cedillo Tr. at 1139, 1142. *See also* Cedillo Tr. at 1847-51 (Dr. Ward's testimony explaining why PBMCs were an appropriate substitute for gut tissue).

[368] Y. D' Souza, *et al., No Evidence of Persisting Measles Virus in Peripheral Blood Mononuclear Cells From Children With Autism Spectrum Disorder,* PEDIATRICS 118(4): 1664-75 (2006). Doctors Fombonne and Ward were co-authors on this study.

Doctor Hepner's criticisms were answered in the second D'Souza paper.[369] This study used gut tissue, the Uhlmann and Kawashima primers, and the same procedures as the Uhlmann and Kawashima investigators. It also involved the use of F gene probes, developed by Dr. Ward's laboratory, and sequencing of the product of the PCR processes.

When Dr. Ward's group tested the Uhlmann primers on gut tissue, they obtained results similar to those reported by Dr. Uhlmann, including similar copy numbers. However, only some of those samples had appropriate melt curves, and none had bands in the appropriate location during the gel electrophoresis of the F or H genes.[370] Two of 17 had appropriate bands when the N gene assay was performed. When the results were sequenced, the results were compatible with various mammalian genes, including a human gene, but not measles virus. Cedillo Tr. at 1859-61, 1909A-12A.

Using the Kawashima F gene assay, ten samples had the correct band size on gel electrophoresis, but when the results were sequenced, nine of the ten were compatible with a human mitochondrial DNA gene, and the remaining sample did not match any genes in the database. None of the samples produced using the Kawashima H gene primer tested positive by nested PCR.[371]

The melt curves indicated the amplification was not specific to the targets. This caused many of the samples to "fall out" of the group of potentially positive results. When the DNA fragments were run on a gel, many of the remaining samples were negative. However, in three of the 42 children with ASD (as compared to none of the 17 controls), the test results remained positive after the gel. If Dr. Ward and his researchers had stopped at this point, they would have reached conclusions similar to those in Dr. Kawashima's study. However, Dr. Ward's laboratory used a slightly different technology for detecting the end products, and then sequenced the genes from the positive results. Upon sequencing, all of the gene products, obtained by using the Uhlmann F, N, or H primers, turned out to be human genes, not measles virus genes. No measles virus genomic material was found. Cedillo Tr. at 1850-53.

The sequencing results demonstrated a problem with the primers. Further investigation revealed that the F-1 Uhlmann primer had an 85% homology with a

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[369] Y. D'Souza, *et al.*, *No Evidence of Persisting Measles Virus in the Intestinal Tissues of Patients with Inflammatory Bowel Disease,* GUT 56: 886-88 (2007), filed as Cedillo Res. Ex. BB, Tab 29. Doctor Ward was a co-author.

[370] Doctor Hepner agreed that the lack of band specificity meant that the primers were amplifying cDNA from something other than the measles virus. Cedillo Tr. at 644-45.

[371] Nested PCR involves a PCR reaction performed on material previously amplified by PCR, using one set of primers for the first reaction and another set of primers for the second reaction. It greatly increases the chances of contamination, making negative controls absolutely essential to obtaining scientifically valid results. Cedillo Tr. at 1958A; Snyder Tr. at 896A.

particular human gene, explaining both the blurry bands on the gels and the incorrect melt curves. The primers could bind to human genes and result in the amplification of human gene sequences, rather than the measles virus they were designed to target. Cedillo Tr. at 1853-55. Sequencing revealed a problem that, otherwise, would not have been detected. Cedillo Tr. at 1856A-57A.

In contrast, none of the gut samples tested positive for measles virus using the Ward laboratory's F gene assay. Cedillo Tr. at 1859A-60A; Cedillo Res. Ex. BB, Tab 29, at 886. Sequencing demonstrated that the Uhlmann primers were amplifying human, not viral, genes. The positive test results at Unigenetics on positive controls indicated that the Uhlmann primers could amplify measles virus. Confirmatory testing by Southern blot of a positive control specimen after using the Uhlmann primers would also produce a result compatible with the presence of measles virus genomic material. Cedillo Tr. at 1850, 1853A-55. However, because the Uhlmann primers were not specific enough, they amplified both measles viral material and human genomic material. The copy numbers are, therefore, immaterial, because high copy numbers could be reflective of human genomic material, rather than measles virus. Snyder Tr. at 964A-66A.

The D'Souza papers were highly praised by a commentary published in Pediatrics in 2006.[372] The author assessed the articles as demonstrating "that the laboratories reporting the measles component findings were in error," and called the studies "exquisitely conducted, repeated, and documented to demonstrate the fallacies of these earlier reports as well as the reasons for them." *Id.* at 1745.

Because of the gene sequencing data provided, Dr. Simmonds' report criticized the Kawashima paper, calling it misleading. He noted that the primer sets for different genes gave discordant results for the same samples, and he called the tables provided "sloppy," because they contained different sequences for the H gene. Snyder Res. Ex. P at 113-14.

(b) The Afzal Papers.

Between 2000-2006, Dr. Afzal published a series of papers involving PCR testing of the Wakefield hypotheses of measles virus causation of both IBD and autistic enterocolitis.[373] The 2000 article[374] began with a summary of previous attempts to

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[372] *See* S. Katz, *Has the Measles-Mumps-Rubella Vaccine Been Fully Exonerated?* PEDIATRICS 118: 1744-45 (2006), filed as Cedillo Res. Ex. T, Tab 17. Doctor Katz disclosed his membership on Merck's Vaccine Advisory Board in the article.

[373] In 1999, Dr. Afzal had published a letter in GUT, responding to a proposal that gene amplification and sequencing might provide a definitive answer to the measles-IBD theory. The letter referenced "several published studies" by both his team and "the IBD study group who formulated the original measles hypothesis" that indicated PCR had been used to examine biopsies from Crohn's disease patients, looking for the N, F, and H genes, all with negative results. M. Afzal, *et al., Measles virus and*

identify measles virus in biopsies from patients with IBD by various histological means, noting issues concerning the specificity of reagents and the difficulty in distinguishing virus structure from normal cellular structures. The study itself involved testing PBMCs and biopsies of inflamed bowel tissue from Crohn's disease patients, using primers specific for three different measles genes (N, M, and H). No measles RNA was found in any of the samples. This result was consistent with reports from other researchers, using different PCR methodologies, all of whom had failed to detect measles RNA. The report also refuted a number of hypotheses put forth by Dr. Wakefield's group from the Royal Free Hospital to explain why other researchers could not detect measles virus.

In 2001, the Afzal group published a letter to the editor of Digestive Diseases and Sciences that was highly critical of its 2000 publication of the Kawashima article.[375] The letter commented that other researchers who had failed to find measles virus in biopsies and PBMC of patients with IBD had used "more robust and sensitive methods than the method applied by Kawashima." *Id.* at 658. It also noted anomalies in the gene sequencing data provided by Kawashima when compared with the vaccine strain virus, in addition to noting sequence variations in the same sample amplified by different processes. The authors stated that, "[a]nomalies of this nature, however, are a good indicator of the presence of mixed DNA fragments in the PCR products that are usually produced by cross-contamination with more than one template." *Id*. They also pointed out the discordance observed when samples tested positive for one measles gene, but negative for other measles genes. Doctor Afzal characterized the Kawashima findings as "not internally consistent or consistent with the findings of others and, in our view, are not compelling." *Id*. at 659.

In a 2002 publication, Dr. Afzal summarized the evidence for and against the IBD/autistic enterocolitis and measles virus hypotheses.[376] He proposed an initiative to supply measles virus samples to a number of laboratories, including Unigenetics, to determine whether the laboratories could reliably detect measles virus in tissue. Unigenetics declined to participate. *See* M. Afzal, *et al.*, *Comparative evaluation of measles virus-specific RT-PCR methods through an international collaborative study,* J.

Crohn's disease, GUT 44(6): 896-97 (1999), filed as Cedillo Res. Ex. BB, Tab 2. It appeared from the letter that the "IBD study group" may have been Dr. Wakefield's Royal Free Hospital group. *See* Cedillo Res. Tr. Ex. 7 at 2 (letter signed by Dr. Wakefield identifying him as the head of the Royal Free IBD study group).

[374] M. Afzal, *et al.*, *Further Evidence of the Absence of Measles Virus Genome Sequence in Full Thickness Intestinal Specimens from Patients with Crohn's Disease*, J. MED. VIROL. 62(3): 377-82 (2000), filed as Cedillo Res. Ex. BB, Tab 1.

[375] M. Afzal, *et al., Measles Virus Persistence in Specimens of Inflammatory Bowel Disease and Autism Cases,* DIG. DIS. SCI. 46(3): 658-60 (2001), filed as Cedillo Res. Ex. BB, Tab 3. Doctor Hepner criticized the Afzal studies for using primers different from those used by Dr. Uhlmann. Cedillo Tr. at 643.

[376] *See* M. Afzal and P. Minor*, Vaccines, Crohn's disease and autism,* MOL. PSYCHIATRY 7: S49-50 (2002), filed as Cedillo Pet. Ex. T, Tab 1.

MED. VIROL. 70(1): 171-76 (2003) ["Afzal 2003"], filed as Cedillo Res. Ex. V, Tab 1 at 175 (noting Unigenetics' non-participation in the subsequent study); Cedillo Tr. at 2034, 2057A-59.

However, Dr. Kawashima's laboratory did join six other laboratories in participating in Dr. Afzal's proposed study.[377] Each laboratory was provided four different inflamed gut biopsies as the unknown samples. Confirmed negative samples from four Crohn's disease patients were prepared in duplicate; one of the duplicates was spiked with measles virus. The participating labs were blinded as to the status of the samples. The laboratory with the most discordant results was Dr. Kawashima's. *See* Cedillo Res. Ex. V, Tab 1, Table III. The samples with high copy numbers were those where the seven laboratories were most consistent in their results; those with low copy numbers were less reliably identified. The assays used in the seven laboratories were different, and there was significant variability in sensitivity. Cedillo Tr. at 632A-34A.

The last Afzal study[378] filed was published in 2006, and involved the use of conventional PCR, nested PCR, and TaqMan PCR in an attempt to detect measles virus in the PBMC of autistic children who had received MMR vaccinations. All of the children had detectible measles antibodies (reflecting exposure to the virus or receipt of the vaccine), but none tested positive for the presence of the virus itself, in spite of the use of very sophisticated PCR techniques.

(c) Doctor Chadwick's Efforts.

Prior to Dr. Wakefield's association with Dr. Kawashima, Dr. Chadwick (who was then working on his Ph.D thesis with Dr. Wakefield as his primary supervisor) had attempted to detect the presence of measles virus in PBMCs, but was unable to do so. He used PCR to test PBMCs of children with autism for the presence of both the H and N gene, but did not find the virus. He was surprised that Dr. Kawashima was able to detect the presence of the H gene in PBMCs. Cedillo Res. Ex. QQ at 2-3.

During the course of Dr. Wakefield's association with Dr. Kawashima, Dr. Chadwick sent samples to Dr. Kawashima for testing. On one occasion, Dr. Kawashima reported positive results for measles virus in samples that Dr. Chadwick had previously tested with negative results. Doctor Chadwick performed gene sequencing on the positive samples, and discovered the sequence was identical to that of the positive control SSPE samples he previously provided to Dr. Kawashima. The patient samples were contaminated with material from the positive control. Doctor Chadwick notified Dr. Wakefield of the contamination. Cedillo Res. Ex. QQ at 3.

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[377] Afzal 2003, filed as Cedillo Res. Ex. V, Tab 1.

[378] M. Afzal, *et al., Absence of Detectable Measles Virus Genome Sequence in Blood of Autistic Children Who Have had Their MMR Vaccination During the Routine Childhood Immunization Schedule of UK,* J. MED. VIROL. 78(5): 623-30 (2006), filed as Cedillo Res. Ex. BB, Tab 4.

(2) Failure to Use Blinded Samples.

One of the principal criticisms of the Uhlmann study was, as both Drs. Ward and Griffin noted, the failure to use blinded samples.[379] Cedillo Tr. at 1846, 2863. When the samples are not blinded, the potential for manipulating the data exists, as noted in Part G.5.e.(4)-(5), below.

(3) Data Omitted.

Dr. Bustin offered several criticisms of the Uhlmann paper concerning omitted data, including: (1) no information regarding amplification sensitivity or efficiency; (2) no information regarding the testing on the positive and negative controls; and (3) no information concerning the quality of the RNA used. He also criticized the study because no standard curve was developed. Cedillo Tr. at 1951A-52A.

The Uhlmann paper described the use of no-template (negative) controls, but it did not provide sufficient data to determine if the negative controls were functioning properly during the TaqMan assay. Good science dictates that in doing biochemical assays, including PCR, the results of the controls should be reported. Otherwise, a reviewer cannot assess the reliability of the results from testing the unknown samples. Cedillo Tr. at 1940-41; Cedillo Res. Ex. UU at 5.

Doctor Bustin noted that, contrary to the standard practice in this field, the Uhlmann paper did not provide information about how the RNA was handled or extracted, its quality, or the quantity present. Cedillo Tr. at 1945A-46. Although the results were based on both fresh-frozen and formalin-fixed samples, the paper provided no information distinguishing the samples, or whether the same percentages of each type were used for controls and samples. This information is crucial in evaluating the reliability and validity of the data generated. Cedillo Tr. at 1947A-49A.

(4) Quality of RNA Samples.

The Uhlmann paper reported on 91 cases. Doctor Bustin indicated that, based on the quality of the RNA reported, only 56 met quality standards for testing.[380] Of these 56 samples, 35 were positive for the F gene upon testing, indicating that the F gene target was amplified. Doctor Bustin was careful in his testimony to distinguish between amplification of the F gene target, and the actual presence of F gene in the samples. Cedillo Tr. at 1996-98.

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[379] The Uhlmann paper was silent on whether the investigators were blinded as to the source of samples. Doctor Griffin testified that if they were working with blinded samples, the article would have said so. Cedillo Tr. at 2866.

[380] In his testimony, Dr. Bustin made a small arithmetic error, and testified that only 55 samples met quality standards for testing. Cedillo Tr. at 1997.

(5) Doctor Oldstone's Experience.[381]

After the *Cedillo* trial, Dr. Ward approached Dr. Oldstone and informed him that one of his articles was being used to support the proposition that autism is caused by measles virus. *See* Part F.2.b.(1), *supra*. In response, Dr. Oldstone recounted his experience with Drs. Wakefield and O'Leary to Dr. Ward.[382] According to Dr. Ward, Dr. Oldstone was approached about a collaboration with Dr. O'Leary, but, before he would agree to collaborate, he wanted to ascertain the O'Leary laboratory's ability to detect reliably measles virus. He therefore prepared tissue and cell cultures at various levels of infection, and sent blinded samples to the O'Leary laboratory. After the laboratory tested them, Drs. Oldstone and O'Leary unblinded the specimens and determined that the laboratory results were only about 80% accurate, including about 10% false positive results. Snyder Tr. at 952A-56A. According to Dr. Ward, this result would be unacceptable in a research setting, and was wildly inappropriate for a diagnostic lab, such as Unigenetics. Cedillo Tr. at 1846; Snyder Tr. at 956A.

Doctors Oldstone and O'Leary agreed to try again, and Dr. Oldstone prepared another set of samples. After testing, the results were jointly unblinded, with a similar level of inaccuracy of around 20%. Some of the samples that were false positives or false negatives in the first round of testing were resubmitted in the second round with new code numbers. In several instances, samples that tested as positive during the first round tested negative in the second, and vice versa. At that point, Dr. Oldstone decided against any further collaboration, and suggested publishing the results. However, the study's sponsor would not grant permission for publication. Snyder Tr. at 957-58A.

Although it is possible that contamination of the samples submitted occurred in Dr. Oldstone's laboratory, a position advanced by Dr. Kennedy, Dr. Ward discounted that possibility. He noted that Dr. Oldstone was considered a meticulous scientist, with

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[381] Because Dr. Oldstone did not testify, I considered this evidence to be less reliable than the other evidence that challenged the O'Leary laboratory's findings. However, Dr. Ward's testimony about his conversations with Dr. Oldstone substantiated other evidence that Unigenetics' results were not reliable, and for that reason, I considered it relevant. I also note that petitioners' counsel elicited similar hearsay from Dr. Kennedy, concerning his conversations with Dr. Sheils (*see* Snyder Tr. at 331A-36A), to establish the reliability of Unigenetics. Hearsay is permissible under the relaxed evidentiary standards in Vaccine Act cases. *See* § 300aa-12(d)(2)(B). Doctor Oldstone's experience with Unigenetics was also recounted in evidence presented to Congress in 2001. *See Autism - Why the Increased Rates? A One-Year Update: Hearings before the Committee on Government Reform*, 107 Cong. 29 (2001) at 174-75 (testimony of Dr. Michael Gershon regarding Dr. Oldstone's testing of Unigenetics' ability to detect measles virus by PCR) (available at frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=107house_hearings&docid=f:76856.pdf) (last visited January 22, 2009).

[382] After conversing with Dr. Oldstone about the aborted collaboration with Dr. O'Leary, Dr. Ward sent his notes to Dr. Oldstone. Thereafter, Dr. Oldstone wrote a letter, filed as Snyder Res. Ex. AA, setting forth his recollections of the events. Snyder Tr. at 962A. Petitioners objected to the portion of Dr. Oldstone's letter that set forth his opinion on vaccine causation of autism as an untimely filed additional expert report, but did not otherwise object to the letter. Snyder Tr. 11-12.

a 50-year track record of high quality and high impact publications. Snyder Tr. at 959. Doctor Kennedy also suggested the misidentified samples were probably at the low end of the detection threshold (Snyder Tr. at 337A-39A), but his explanation did not account for false positive results nor how the same samples could test positive initially, but negative when submitted a second time, or vice versa. Snyder Tr. at 960A-62A.

Doctor Griffin summed up the criticisms when she testified that the reputation of the O'Leary laboratory in the scientific community was "not very good." Cedillo Tr. at 2866.

The evidence that Unigenetics was not reliably detecting measles virus is highly probative. The lack of specificity in the F gene primers and the resultant amplification of DNA from sources other than the measles virus, the discordant results for H and N genes, the failure to sequence the results from the F gene positives, and the inability of other laboratories to reproduce its results all cast considerable doubt on the reliability of Unigenetics' reports. Therefore, based on evidence not derived from the U.K. litigation materials, I conclude that Unigenetics' reports cannot be considered at face value and are entitled to little evidentiary weight, absent some indication that a specific test result is corroborated by evidence from sources other than Unigenetics. I address additional problems with Colten's Unigenetics test results in Section VIII, below.

e. The U.K. MMR Litigation Data.

Respondent filed a number of documents and expert reports containing information derived from the U.K. MMR litigation, including the expert report of Dr. Peter Simmonds,[383] two reports by Dr. Bustin,[384] and a report by Dr. Rima.[385] In addition, some of the testimony of Dr. Bustin and Dr. Rima was derived from information they acquired in the course of that litigation. As a part of the U.K. litigation, Dr. Bustin was given access to all of the raw data underlying the Uhlmann paper as well as the information on the assays carried out for the U.K. litigants. Doctor Rima was also provided access to background materials regarding testing.

At the request of the U.K. court, Dr. Bustin conducted a review of the Unigenetics laboratory, which involved an examination of data underlying their results and two site visits.[386] Asked to summarize his chief concerns, Dr. Bustin testified that there was

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[383] His report was filed as Snyder Res. Ex. P.

[384] His June 2003 report was filed as Snyder Res. Ex. Q. His November 2004 report was filed as Snyder Res. Ex. R.

[385] Doctor Rima's report was filed as Snyder Res. Ex. S.

[386] Doctor Bustin testified that he was approached by attorneys for GlaxoSmithKline in June or July of 2003, who asked him to look at the Uhlmann paper and some of the documentation provided by Dr. O'Leary and Unigenetics in response to discovery requests in the U.K. litigation. He was told he was a "Court witness," rather than a partisan advocate, and he approached his analysis of the evidence in that

clear evidence that the laboratory was detecting a DNA contaminant, not measles virus RNA. He therefore concluded that there was no measles virus in any of the case samples that Unigenetics tested. Cedillo Tr. at 2035-36. His testimony further detailed the reasons he believed the laboratory could not reliably report the presence of measles virus RNA in tissue, blood, or CSF.

Doctor Rima shared Dr. Bustin's opinion. He flatly stated that he had no confidence in the results from the Unigenetics laboratory. Snyder Tr. at 846A. His criticisms of the Unigenetics laboratory were based on evidence he found indicating carelessness and on practices he found "unacceptable as a scientist." Snyder Tr. at 927A. Doctor Rima identified his top three problems with the Unigenetics laboratory: (1) reporting discordant results as positive, a procedure he characterized as seriously inconsistent with normal scientific procedure; (2) failing to optimize the F gene assay; and (3) using TaqMan PCR under sub-optimal conditions.

The evidence from the U.K. MMR litigation established that Unigenetics experienced all of the problems commonly encountered in PCR testing, and that it failed to take adequate measures to detect and correct them. In addition to the problems in the primers used to select the amplification target addressed by Dr. Ward, other problems with the primers were discovered. Unigenetics had problems in RNA extraction and sample quality, poor internal controls and poor adherence by laboratory personnel to Unigenetics' own SOP, unblinded testing that permitted data manipulation, and a critical problem with contamination. Some of the data discovered during Dr. Bustin's review suggested a fraudulent manipulation of laboratory notebooks and machine settings. Other evidence generated during the U.K. litigation demonstrated anew that Unigenetics' results could not be reproduced. Although there was testimony that Unigenetics sequenced some of the cDNA obtained through PCR, no results of sequencing have ever been published. Unigenetics attempted to use allelic discrimination to identify vaccine strain measles virus without sequencing; Dr. Rima's examination of the underlying data indicated that the results of their allelic discrimination testing were not reliable. Respondent's experts carefully and persuasively explained why even Unigenetics' high copy number results were not a reliable indicator of measles virus in the samples reported.

(1) Quality of Samples.

Doctor Bustin assessed the Unigenetics practice with regard to quality and

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light. Cedillo Tr. at 1962A-64A. He was granted access to the Unigenetics laboratory in January and May, 2004. Cedillo Tr. at 1964A. He analyzed the raw data files from Unigenetics, an operation that involved about 1500 hours of work. He looked at all the notebooks disclosed in the course of the litigation, statements from all the Unigenetics laboratory workers, the expert witness reports filed by Drs. O'Leary and Sheils, all of the operator sheets produced during discovery, all the experimental reports produced, and the laboratory's SOP. Cedillo Tr. at 1964A-68A. In addition, he analyzed the data files directly on Unigenetics' own computers. Cedillo Tr. at 1965A-66A. I found Dr. Bustin to be a candid, forthright, and compelling witness.

quantity assessment of RNA in samples as inconsistent. He found very little quality assessment was performed. Even when quality assessment was done, it was often done improperly, resulting in the testing of samples that should have been discarded. Data from the Uhlmann paper indicated that, in approximately one-third of the samples tested, the RNA quality was unacceptable for PCR. Cedillo Tr. at 1996-97.

In analyzing the materials produced, Dr. Bustin noted that Unigenetics' reported comparisons of the quantity of RNA produced from formalin-fixed tissue versus fresh-frozen tissue were generally appropriate. It took approximately 25 cycles to produce a specific amount of RNA (the "copy number") from fresh-frozen tissue samples and about 35 to 45 cycles to produce it from formalin-fixed samples. These results indicated that there was approximately 200-300 times less of the target RNA in the formalin samples than in the fresh samples. Doctor Bustin illustrated this difference in Cedillo Res. Tr. Ex. 13 at 5.

However, when he analyzed the results from a specific control sample[387] amplified by the laboratory, the copy numbers from fresh-frozen tissue and formalin-fixed tissue were not noticeably different. The cycle numbers were the same, in spite of the presumed lower quality of the DNA in the formalin-fixed sample. This anomalous result indicated that whatever was being amplified in the formalin-fixed sample was a contaminant introduced after the fixation. Cedillo Tr. at 1971A-73.

The RNA extraction phase is crucial to the results because the quality of the RNA determines the results. Poor quality RNA will result in low copy numbers; high quality RNA will result in higher copy numbers. Unigenetics ostensibly applied two quality control measures. The first check involved looking at the ratio of two optical densities, which could identify contaminants in the RNA sample. Unfortunately, this test was not routinely performed.

The other quality assessment method involved the measurement of GAPDH, a cellular reference gene, detectable if the RNA is of good quality. Every cell in the human body expresses this gene and, thus, it can be used to determine whether an RNA extraction actually contains RNA. If the reference gene cannot be detected, the sample should not be analyzed, because there is no RNA present. Unigenetics' laboratory SOP acknowledged this principle by stating that if GAPDH were not present, the sample should not be analyzed. However, laboratory personnel did analyze samples where the reference gene could not be detected. When positive results for the F gene were obtained from samples with no detectable GAPDH, the results reflected contaminant, not measles virus. Cedillo Tr. at 1973-75A 1978A-79A, 2054.

Additionally, the conversion of RNA to cDNA had hallmarks of "operator error," as the conversion step was sometimes skipped, rendering any results useless. During Dr. Bustin's review of the Unigenetics laboratory data, he began to think that the

[387] The control sample was from an SSPE patient.

positive laboratory results for measles virus genes were the result of contamination, rather than the actual presence of the virus in the unknown samples. His slides, Cedillo Res. Tr. Ex. 13 at 8-9, reflected Unigenetics laboratory data that demonstrated the reverse transcription step had not been performed. The results on page 9 of this exhibit indicated that in four of the lead cases in the U.K. litigation, the laboratory failed to perform reverse transcription. The positive results could not have come from the patient samples because any RNA present in them was not converted to DNA. Because PCR cannot amplify RNA, whatever was amplified had to be a contaminant introduced in the laboratory. Cedillo Tr. at 1980A-82.

(2) Primers.

As noted in Part G.5.d., above, Unigenetics' F gene primer was not sufficiently specific. During Dr. Bustin's examination of Unigenetics' data in the U.K. litigation, he discovered another issue with the primers. The laboratory used primers for both the F and H genes and attempted to optimize their assays for both, with the goal of developing concordant results. Unigenetics found that the H gene assay was much more sensitive than the F gene assay. In testing the same tissue, on some occasions they obtained positive results for the F gene, but obtained negative results on the more sensitive assay for the H gene. Faced with this problem, the laboratory should have redesigned the F gene assay in order to have concordant results. Instead, Unigenetics ignored the negative H gene results, and reported only the positive F gene results. Cedillo Tr. at 1985A-86A.

(3) Controls and Standards.

Approximately one-third of Unigenetics' runs had positive results for the negative controls, a result indicative of a significant problem with contamination. In at least one case, an environmental control (a tube left open to the air in the laboratory) tested positive, a strong indicator that the laboratory itself was contaminated. Cedillo Tr. at 1995-96.

The concerns Dr. Bustin developed about contamination at Unigenetics were heightened when he visited the laboratory and discovered that the PCR portion of the laboratory was next to a room labeled "Plasmid Room." Plasmids are DNA molecules used to replicate large quantities of DNA in a bacterium. These bacteria offer massive potential for DNA contamination, and standard scientific practice would be to place the plasmid facility as far from the PCR laboratory as possible. Plasmids get onto hair, hands, and clothes, and are easily transferred throughout the facility, and extremely difficult to eradicate. Although Dr. Sheils assured Dr. Bustin that they did not use the plasmid room for growing F gene targets, he remained concerned it was the source of the contamination he already had identified in the assays. Cedillo Tr. at 2021-23.

Another issue identified by Dr. Bustin concerned the failure of Unigenetics personnel to follow their own SOP. Doctor Kennedy concurred in the importance of developing and following a laboratory SOP for any PCR experiment, particularly when

PCR results are used in diagnosis. He testified that any variations from the SOP should be recorded in detail, including the reasons for the variation. Cedillo Tr. at 818. Unigenetics personnel failed to do this.

The TaqMan probe contains a fluorescent label. In addition to this fluorescence, a reference dye (called ROX) is added to each tube to ensure correct pipetting of the sample. The PCR instrument recognizes ROX and compensates for varying quantities of the substance. Doctor Bustin examined the ratio of the fluorescent probe to the ROX dye in the reaction tubes. If the investigator placed the same amount of probe into each tube, ROX amounts should be roughly the same across the plate. Cedillo Tr. at 2024-25A. The chart at Res. Cedillo Tr. Ex. 13 at 19, indicated that, in 18 wells, twice as much probe was added than in the remaining wells because the ratio of probe to ROX dye was increased in those 18 wells from approximately .65 to 1.3. This incorrect pipetting was just one example of many deviations from the lab's own SOP found by Dr. Bustin. Such deviations lead to inconsistent results. Cedillo Tr. at 2025A-26.

To quantify the amount of measles virus in any given sample, Unigenetics developed a standard curve. The "CT" (sometimes referred to as "Ct") number on data generated to support quantification represented the number of cycles of amplification performed before detecting the target gene. The lower the amount of the target gene in the sample, the higher the number of cycles required before getting a positive reading. Because the unknowns reflected on Cedillo Res. Tr. Ex. 13 at 10 were not within the parameters of the standard curve, it was impossible to quantify the amount of F gene in these unknown samples, and a copy number should not have been reported. Cedillo Tr. at 1992-94.

Cedillo Res. Tr. Ex. 13 at 10, also illustrated the difficulty Unigenetics had in applying their results to their standard curve. In this exhibit, the unknown samples (the red dots) were clustered on the standard curve line, but outside the ranges as defined by the black dots of the standards. The right side of the standard curve reflected the highest concentrations of known F gene RNA and involved a cycle count of 15. At a tenfold dilution (the second black dot), the cycle number was 18; at another tenfold dilution, the threshold cycle was 21. Cedillo Tr. at 1989A-91A. All of the unknown samples in this exhibit appear to the left of the last data point on the standard curve. They were actually out of range and the laboratory should not have reported any quantity of measles virus. Cedillo Tr. at 1991A.

The standard curve at Cedillo Res. Tr. Ex. 13 at 11, illustrated the difficulty Unigenetics encountered in amplifying low copy numbers. One of the known standards was significantly diluted, and after 45 cycles of amplification, the laboratory was unable to detect the presence of virus under optimal conditions. This indicated that the assay was working very poorly, and thus the quantifications of the other samples in this run were meaningless. Cedillo Tr. 1994-95. If less than 20,000 copies of the target F gene existed in the tested material, Unigenetics was unable to amplify DNA. Cedillo Tr. at 1992-94.

(4) Unblinded Testing.

Problems from the use of unblinded data were illustrated in the way Unigenetics handled settings on their PCR machines. An example of the results from one of their machines is shown on Cedillo Res. Tr. Ex. 13 at 12. The fluorescence threshold is the line running from left to right across the middle of the graph. The first cycles (on the far left side of the graph) contained random "noise," and, therefore, the manufacturer recommended that the first three cycles be excluded from analysis. Beginning at about cycle 17 and continuing to about cycle 26, four curves appear, supplemented by red lines. These lines are virtually parallel, indicating that similar amplification of the target occurred. Because they are similar, the copy numbers can be reliably compared. These are samples containing more of the target.

A very well-designed assay would demonstrate linear results, but with higher numbers of cycles, the assay becomes less efficient. This was reflected by the two red lines on the far right of the graph in Cedillo Res. Tr. Ex. 13 at 12. Cedillo Tr. at 2001-05. The curves on the far right side of the graph that failed to reach the fluorescence threshold were recorded as negatives, a subjective assessment. If the samples represented by these curves contained the targeted gene, they were false negatives. If they were "no-template" controls, something in the negative control was being amplified and should have been reported as positive. This example illustrates the role that subjective analysis properly plays in interpreting PCR results. Cedillo Tr. at 2004A-05.

However, Unigenetics used subjective assessments improperly. It set the threshold cycle of its machines in what Dr. Bustin called "a very peculiar way," sometimes using the manufacturer's guidelines and sometimes not. Cedillo Tr. at 2005. An example of a Unigenetics printout from their ABI 7700 machine is found at Cedillo Res. Tr. Ex. 13 at 13. The printout reflects the use of the ABI standards, with the baseline starting at number 3 and going up to 15. The red and green lines reflect results from two different samples, with the red line sample crossing the threshold at 33 cycles and the green line crossing the threshold at 37 cycles. Cedillo Tr. at 2005-06.

If no subjective analysis were applied to these results, both would be read as positive. However, the curves reflected very different slopes. The red line showed an appropriate curve; the green line wobbled up and down at the threshold. After examining this result, a blinded reviewer would have concluded the sample reflected by the green line should not be read as positive. Unigenetics reported both samples as positive. Unigenetics frequently reported positive results from samples that should have been read as negative. Cedillo Tr. at 2005-07.

Unigenetics' practice on reporting discordant results from the same sample was decidedly unusual. It is standard practice to test samples at least twice. If the results are genuine, they will be the same. If there are discrepancies, the test should be repeated. Unigenetics ran assays in duplicate and sometimes in triplicate, but in many instances, the results for the F gene were discordant, with one test positive and one test negative, and with different cycle numbers. Cedillo Tr. at 2013-14.

The results of one repeated assay are displayed in the slide appearing at page 16 of Cedillo Res. Tr. Ex. 13. The open bars reflect the assay run on March 21, 2003, and the solid bars reflect the repeated assay done on March 26, 2003. Doctor Bustin noted the massive variability in the cycle numbers obtained on the different dates for the same samples. He pointed out that some of the samples tested positive on the first run and negative on the second, and vice versa. Unigenetics reported the samples that tested positive on either day as positives, ignoring the discordant results. Cedillo Tr. at 2014.

Doctor Bustin also testified that an ABI 7700 machine used by Unigenetics was defective. The heating block for the ABI 7700 contained 96 wells, permitting the operator to run 96 assays at a time, but heating and cooling were not uniform across the block in these machines. For that reason, investigators aware of the heating problem do not use the outside wells. The machine that was used on most of Unigenetics' runs had huge variations in the heating and cooling across the block. Depending on where the tube was placed, the temperature fluctuations caused variability in the results because both reverse transcription and PCR are sensitive to temperature. Unigenetics was unaware of the problem with the ABI 7700 machines. Cedillo Tr. at 1998-2000.

(5) Evidence Suggesting Fraud.

Laboratory notebooks are used to record what is done in an experiment, and are later used to write papers on the experiment. Laboratory notebooks are generally available for inspection. In standard practice, notebook entries are usually made relatively contemporaneously and are not, thereafter, changed. Cedillo Tr. at 2026-27.

During the course of the U.K. MMR litigation, the same laboratory notebook was disclosed on two separate occasions. Cedillo Tr. at 2027. As indicated in Cedillo Res. Tr. Ex. 13 at 20, and in Dr. Bustin's accompanying testimony, the top laboratory notebook page was disclosed at the earlier of the two occasions. The second page, the same notebook page as the first, was disclosed at a later time. It contained parenthetical additions, which Dr. Bustin charitably called "unusual." Cedillo Tr. at 2027-28.

The second disclosed page contained the phrase "A10 tipped," which refers to the end of a pipette tip being brushed against a reaction vessel, thus putting a small bit of the reaction mix into the wrong tube. This would be a plausible explanation for a false positive result, if made contemporaneously with the event. The later addition of this parenthetical suggests something less benign than such an error. This was only one of several examples of alterations Dr. Bustin found in laboratory notebooks.[388] Cedillo Tr. at 2028-32.

[388] Doctor Rima also observed this alteration, but it was the only alteration in a notebook of which he was aware. Snyder Tr. at 855A-56A.

Another example of an alteration in a submitted document was found in Cedillo Res. Tr. Ex. 13 at 21-22 (page 22 is an enlarged version of a segment of the document appearing on at 21). The document listed the date of the run, the experimental conditions, what wells were used, and the nature of the substance in each well. Doctor Bustin determined that each sample in this run was a triplicate, with three wells used for each sample. The wells (identified by the letter A, B, or C in the left column) each had a number identifying the sample in the left center of the page. Wells B1, B2, and B3 were all from Sample 1 (identified in the fourth column from the left). The fifth column from the left indicated the results; the sixth column indicated the quantity of the target substance. The entries in the sixth column were roughly the same for each group of three samples, confirming that the run was made in triplicate. Cedillo Tr. at 2029-31.

Unigenetics submitted testing data for the U.K. litigants to the court with each case in the litigation assigned a unique number. When documents such as the page appearing on page 22 of Cedillo Res. Tr. Ex. 13 were submitted as evidence, Unigenetics personnel would mark the results relevant to a particular litigant by boxing them in and writing the litigant number next to the result. In this particular exhibit, the results relevant to wells C1 and C2 were boxed in, with a handwritten "# 8" inside the box, indicating that these two wells pertained to Patient Number 8 in the litigation.[389] The handwritten notation "viral cells 1/100" was also written by Unigenetics personnel, reflecting that these were positive controls–cells known to be infected with measles virus at a 1/100 level of infection. The entry in column three for these two wells is "Positc," an abbreviation for "positive control." Because Dr. Bustin received this document from evidence relating to Patient Number 8 in the U.K. litigation, he interpreted the entries as an attempt to report the results from a positive control as a litigant's result. Cedillo Tr. at 2031-32. In essence, Unigenetics took a control sample known to contain measles virus and reported it as a litigant's sample, the PCR testing equivalent of "planted evidence."

The bottom slide on Cedillo Res. Tr. Ex. 13 at 14 reflected another problem with Unigenetics's reporting. The baseline on slide B reflected a range of 2-13, rather than the 3-15 range recommended by the manufacturer. The effect of using the altered range was to change the results from positive to negative. This is significant, because the sample in question was a negative control. If it tested positive, suggesting contamination, it would raise doubts as to the other results from the same run. Using the manufacturer's settings, as Slide A of this exhibit demonstrated, the negative control sample should have returned a positive result. Cedillo Tr. at 2008-10A.

Although Dr. Bustin stopped short of saying the alteration in the settings was a deliberate manipulation of the data, he testified that the unusual settings were a matter of curiosity for him, until he obtained access to the raw data, which showed this

[389] Doctor Bustin testified that he added brackets to the third column, reflecting the triplicate run in each bracket. He also added the handwritten arrow in the middle of the page and the large question mark next to the data from wells C1 and C2. Cedillo Tr. at 2031.

particular sample was a negative control. The clear implication from his testimony was that the raw data provided the motive to manipulate the machine settings, as a positive result for a negative control reflects a contamination problem that should cause all of the samples from that run to be discarded. Cedillo Tr. at 2011A-12. He added that whenever there was a hint of a positive result for the F gene in a sample, regardless of whether the curve suggested actual amplification, Unigenetics called the sample positive. However, when the sample was a no-template control that should have been read as positive, it was either omitted from the report, or the baselines were altered to generate the impression of a negative test. Cedillo Tr. at 2012.

(6) Reproducibility of Unigenetics' Results in U.K. MMR Litigation.

Several witnesses also testified about attempts within the context of the U.K. MMR litigation to confirm Unigenetics' results. During the course of the U.K. litigation, the remaining quantities of Unigenetics' samples were split between the respondents and the claimants and retested. Doctor Simmonds retested samples for the defendant drug companies and Doctor Cotter retested samples for the claimants. Snyder Tr. at 896A

According to Drs. Bustin and Rima, neither Dr. Simmonds nor Dr. Cotter was able to find evidence of measles virus in the claimant samples. Snyder Tr. at 895A-897A. According to Dr. Kennedy, Dr. Sheils told him that Dr. Cotter confirmed the presence of measles virus in the high copy number samples, but she did not provide him with the data. Snyder Tr. at 347A-49A. Doctor Kennedy indicated that information confirming this was in the U.K. litigation files, which were still sealed. Snyder Tr. at 349A-50A.

Doctor Bustin testified that he and Dr. Cotter, whom he described as a PCR expert, worked for the same institution. Cedillo Tr. at 1967A. Using the same type of ABI machine used by Unigenetics, Dr. Cotter attempted to verify Dr. O'Leary's results. Snyder Tr. at 2015A. Using RNA that he personally extracted, Dr. Cotter performed PCR amplifications. In every instance where he used PCR that he extracted, Dr. Cotter obtained negative results. In using Unigenetics' extracted RNA, he obtained positive results, shown on Slide 17 of Cedillo Res. Tr. Ex. 13. The numbers appearing on that slide are the threshold cycle (CT) numbers; red reflects positive results; and green reflects negative results. Cedillo Tr. at 2015A-16. All of Dr. Cotter's extractions from the same sources had previously tested negative. The results reflected on this slide indicated two things. First, Dr. Cotter's assay was more sensitive, because his cycle numbers were lower than Unigenetics'. Second, because samples from these individuals tested negative when Dr. Cotter extracted the RNA, but positive when he performed testing on Unigenetics' extractions from the same individuals, Unigenetics' samples were likely contaminated. Cedillo Tr. at 2016. It was obvious from the slide and from Dr. Bustin's testimony that he had access to Dr. Cotter's data, and did not merely obtain his information through a conversation. Doctor Rima's testimony about Dr. Cotter's results was similar to that of Dr. Bustin, but less detailed. Snyder Tr. at 895A-97A. Doctor Simmonds' report noted that the only two samples of PBMCs that

tested positive for measles virus by Dr. Cotter were extractions performed by Unigenetics, while the corresponding samples Dr. Cotter extracted were negative. Snyder Res. Ex. P at 86-87. *See also* Cedillo Res. Ex. BB, Tab 23 (newspaper article reporting that the claimants' retesting expert was unable to confirm Unigenetics' results).

Based on the testimony and reports, I conclude that the accounts of Drs. Bustin and Rima are more likely to reflect accurately Dr. Cotter's efforts to reproduce Unigenetics' results. However, because the evidence is in conflict, and Dr. Kennedy clearly asserted that evidence contained in the U.K. files would validate his testimony, in an abundance of caution, I have disregarded the testimony about Dr. Cotter's results. I emphasize that I am doing so with great reluctance, in view of the fact that petitioners have not attempted to obtain Dr. Cotter's report from the U.K. court. I am unlikely to disregard this testimony in future cases, absent good faith efforts to obtain the evidence to which Dr. Kennedy referred.

I have, however, considered Dr. Simmonds' report. Using nested PCR, he looked for the N gene and the H gene and was unable to find any positive results for either gene in any of Unigenetics' samples. Snyder Res. Ex. P at 32, 42. As the N gene is normally present at about 30,000 copies per cell (a level seven to eight times higher than the number of copies of the F gene present during an acute infection), it should have been more easily detected. Snyder Tr. at 894A-97A.

(7) Sequencing and Allelic Discrimination.

Based on a conversation Dr. Kennedy had with Dr. Sheils, Dr. Kennedy testified that Unigenetics did sequence their positive results. Cedillo Tr. at 824A. Doctor Ward testified that if Unigenetics had sequenced their positive results, that information was never published. Cedillo Tr. at 1857A, 1912A. Doctor Kennedy concurred that sequencing data had not been published. Cedillo Tr. at 826.

The failure to publish such information is inexplicable, particularly in view of the firestorm of criticism over Unigenetics' testing program. It is equally inexplicable that, if such data existed, petitioners would not have attempted to obtain it. In view of all of the evidence available to me, I cannot credit Dr. Kennedy's testimony on this point.

I add that, in context, Dr. Kennedy's testimony is somewhat ambiguous about whether sequencing was performed on the final product of amplification or whether the "sequencing" to which he was referring was done as a part of Unigenetics' allelic discriminator testing. His actual testimony was:

> A: All Right. Once you've got a positive, yes, you want to sequence. In fact, Dr. Sheils was asked had they sequenced and verified that this was indeed vaccine strain and they had done sequencing of H and F.

Q: Specific to vaccine strain?

A: Specific - - an allelic discriminator from the F. They had actually sequenced the product that came out.

Q: Specific to vaccine strain?

A: Specific to vaccine strain.

Q: And they didn't publish this?

A: This was in - - I had assumed that the Uhlmann paper had already been submitted. So - - and the Uhlmann paper came out --

Cedillo Tr. at 824A-25.

It is not entirely clear from this exchange whether Dr. Kennedy was saying that the positive results themselves were sequenced, or that known vaccine strain and known wild-type measles virus sequences were used to determine whether a sample contained vaccine strain virus. There is hard data to indicate that Unigenetics did the latter; there is none to indicate that they did the former.

Doctor Kennedy's testimony can be read to say that Unigenetics had confirmed the presence of vaccine strain measles virus using an allelic discriminator within the F gene. Cedillo Tr. at 824A, 847. Allelic discrimination is not sequencing. It is a test to determine whether individuals have inherited a parental allele or a mutation. The Unigenetics laboratory attempted to apply allelic discrimination to measles virus under conditions that were experimental. Snyder Tr. at 824A, 847-48. According to Dr. Rima, Unigenetics laboratory was not reliably differentiating between vaccine strain and wild-type measles virus.

Doctor Rima also discussed how the allelic discrimination testing worked with Dr. Sheils, because the materials disclosed to him did not adequately explain the process. Using sequenced data from wild-type virus and vaccine strain virus, Unigenetics designed two probes, one designed to interact only with vaccine strain viral material and one designed to interact only with wild-type virus material. Depending on which virus was present, different fluorescence values would be generated. Snyder Tr. at 856A-57A.

Doctor Rima examined the data underlying Snyder Res. Tr. Ex. 4 at 9, which showed how the allelic discrimination data was generated. The control material for the vaccine test appears in the upper right portion of the lower right square on this exhibit (shown in red). The wild-type virus control material appears in blue in the upper left quadrant of the chart. Controls containing both wild-type and vaccine strain virus RNA appear in green on the slide, in the box in the upper right quadrant of the chart. The remainder of the data points come from claimant samples, which are largely clustered

in the upper left corner of the box labeled “vaccines.” Snyder Tr. at 856A-861A.

Based on his analysis of this data, Dr. Rima concluded that some of the patient samples were misidentified as vaccine strain because replicates of the same sample tested by Unigenetics had different results. If one replicate appeared in the vaccine quadrant and the other appeared in the undetermined quadrant, Unigenetics reported this as a “vaccine strain” sample. This demonstrated that the test they developed was not capable of discriminating between vaccine strain and wild-type strains of the virus. These test results from Unigenetics were never published and this method is not used by other laboratories, other indications that the allelic discrimination test was not an effective method to differentiate between vaccine strain and wild-type virus. Snyder Tr. at 861A-863.

(8) Copy Number Issues.

Doctor Rima disagreed with Drs. Kennedy’s and Hepner’s assertions that the Unigenetics results were problematic only when the reported copy numbers were low. Copy number reporting was subject to the same treatment of discordant results as the results for viral genes, and was affected by the laboratory’s contamination problem. Doctor Rima also testified that discrepancies in the comparison of the GAPDH housekeeping genes and measles virus copy numbers led to incorrect calculations of copy numbers. Snyder Tr. at 869A-71A, 876A-78A.

If Unigenetics detected a number of copies of the virus on one run, but zero copies on a second run of the same sample, they reported the higher number, rather than attempting to determine what caused the discrepancy. Unigenetics’ ignoring of zero values was widespread. Snyder Tr. at 864-65A. The charts appearing on Snyder Res. Tr. Ex. 4 at 2, were taken from Dr. Simmonds’ report, filed as Snyder Res. Ex. P, at 72. The chart on the left reflects the results from two runs of the same sample looking for the measles virus F gene. The datapoint in the upper left hand portion of the chart reflects a value of 5,000-6,000 copies, but the replicate results (the results from the second run) were negative. Unigenetics reported this as a positive result. Snyder Tr. at 865A-68A.

Even when the copy numbers were high, the high values could reflect contamination rather than high amounts of the target substance in tissue. Doctor Rima concurred with Drs. Bustin and Simmonds that the high copy numbers reported were the result of laboratory contamination, rather than high amounts of target virus in tissue. Snyder Tr. at 865A-68A; Cedillo Tr. at 2036, 2065A; Snyder Res. Ex. P at 85-87. In the U.K. litigation, the samples closest to the row in which the high copy numbers were found were the samples most likely to be contaminated. Snyder Tr. at 878A-79A.

In her post-hearing supplemental report in *Cedillo*, Dr. Hepner challenged Dr. Bustin’s testimony that high copy number samples could be the product of “spontaneous” contamination. Cedillo Pet. Ex. 120 at 6. She did not clarify what she meant by “spontaneous” contamination, but the context suggests that she meant

something other than the evidence of widespread contamination found by Dr. Bustin. Her qualification of her opinion, coupled with Dr. Bustin's opportunity to observe the Unigenetics laboratory setting and his access to a substantial amount of information missing from the Uhlmann paper (which was the source of Dr. Hepner's knowledge about Unigenetics operations), causes me to give greater weight to the opinions of Drs. Rima, Simmonds, and Bustin on the effects of contamination on Unigenetics' reported results.

A high copy number of measles virus does not necessarily imply that the threshold cycle (CT) was low. Doctor Rima illustrated this point by reference to the "housekeeping gene" GAPDH, which is present as messenger RNA ["mRNA"] in each cell at about 1,000 copies per cell. Calculation errors involving GAPDH affect the copy numbers reported for the target gene sequences because the reported copy number for the F gene in a given sample is based on the number of copies of the GAPDH gene's mRNA in the same sample. Snyder Tr. at 868A-871A. If a tissue sample were degraded or fixed, it would be more difficult to extract the GAPDH mRNA. In these cases, the GAPDH copy numbers are low, and calculations for measles virus copy numbers that rely on the average cell numbers for GAPDH are unreliable. Snyder Tr. at 873A-75A.

Doctor Rima concluded that when low copy numbers were reported by Unigenetics, the reports were unreliable, because the results were outside the standard curve. Most of the copy numbers reported by Unigenetics were outside their standard curve. Snyder Tr. at 871A-874.

The testimony and other evidence derived from the U.K. litigation confirms the validity of the problems previously set forth concerning Unigenetics' testing. They overwhelmingly establish that Unigenetics' results are so unreliable that they should be precluded from evidentiary consideration. Nevertheless, I have considered them, but given them no weight.

6. The Walker-Hepner "Poster Presentation."

Other than the Unigenetics results, the only laboratory evidence linking gut disorders in children with ASD to measles virus was testimony by Drs. Krigsman and Hepner about research they were conducting to detect measles virus in gut tissue from children with an autistic enterocolitis diagnosis. Doctor Krigsman performed the gastrointestinal biopsies. The RNA was extracted by Dr. Steven Walker, and he and Dr. Hepner developed the reagents and the primer sets for the PCR.[390] Cedillo Tr. at 655A-59, 666. The results of the research had not been published by the time of Dr. Hepner's testimony. If those results have since been published, neither party filed them

[390] The primers used in the Walker preliminary study included the Uhlmann primers, but Dr. Walker redesigned some of them. Doctor Hepner did not specify whether the problematic "F gene" primer was one of those redesigned by Dr. Walker. Cedillo Tr. at 666.

as an exhibit.

Although she qualified the results as "preliminary," Dr. Hepner testified she was successful in amplifying measles virus RNA from many of the bowel biopsies tested. In some samples, the presence of vaccine strain measles virus was "confirmed." Cedillo Tr. at 635A. She was careful to point out that the positive controls for this study were not fully developed, as the investigators did not have a positive control from the wild-type measles virus. Cedillo Tr. at 662A. The point of seeking wild-type virus as a positive control was to permit the laboratory to sequence positive results from the samples as vaccine strain virus, to establish that there was no cross-contamination. In the interim, the positive controls in this study included plasmid DNA. Cedillo Tr. at 667.

Some of the control samples involved postmortem specimens with slightly degraded RNA. Because of the problem procuring appropriate samples for controls, their data was still "very preliminary." Cedillo Tr. at 655A-59. The data available on the negative controls did not indicate whether the samples were from the gastrointestinal tract. Cedillo Tr. at 675.

Leaving aside for the moment the preliminary nature of the results, and the lack of peer review because the results have not been published, a review of the poster presentation and abstract disclosed a number of reasons to accord this study little weight in determining if petitioners have established the presence of measles virus in gut biopsies of ASD patients.

Pages 1-3 of Cedillo Res. Tr. Ex. 13 consisted of pictures taken directly from the Walker-Hepner poster presentation. After reviewing the pictures, Dr. Bustin expressed concern that there was no band in the picture on the right side of page 1 at the level of 726 base pairs. If the run contained measles virus, a band should have appeared at that point. The pictures on pages 1-2 reflected a clear band at about 300 base pairs and at several other points. The presence of these bands indicated a problem with the specificity of the PCR because there were bands where no bands were expected. Additionally, the poster indicated that 12 patient samples were reflected on the gel, with the ladder in lane 13. There were no positive or negative controls; at a minimum, the run should have included a negative control. The lack of a negative control invalidated the results. Cedillo Tr. at 1954A-56A.

Slide number 3 from Cedillo Res. Tr. Ex. 13 contained figure 4 from the poster presentation, which demonstrated the results from nested PCR. The bands were blurred, indicating that the primers were not specific. Once again, there was no negative control, rendering the results meaningless. Cedillo Tr. at 1956A-58A. Doctor Bustin also testified that the use of 35-40 cycles of amplification was high, particularly when using nested PCR. Cedillo Tr. at 1959A.

There are insufficient indicia of reliability in this preliminary work to accord it any weight on the question of whether measles virus truly exists in the gut tissue of children with ASD. As Dr. Ward's description of the preliminary results from his laboratory that

were presented in an abstract, but later determined to be wrong (Cedillo Tr. at 1864A-65) illustrates, there are significant problems inherent in relying upon preliminary and non-peer reviewed work. The poster presentation provides no basis to conclude that the virus is found more often in children with ASD than in their typically developing peers. Unless it can be shown to be an abnormal finding, the presence of measles virus genomic material in the gut tissue of autistic children says little to nothing about possible causation of autism or co-occurring gastrointestinal symptoms and autism. As Dr. Griffin noted in her report, given the extreme sensitivity of PCR testing, viral proteins or RNA might be recovered long after the infectious virus itself has been cleared. Thus, reports of the presence of viral material in these samples, even if accurate, do not warrant drawing a causal connection between measles virus and gastrointestinal symptoms, much less between measles virus and autism. Cedillo Res. Ex. V at 6.

Section VII. Analysis of the Evidence Regarding MMR Causation of Autism.

In the Theory 1 test cases, the PSC chose to present theories of causation restricted to a small subset of children with ASD: those children with regression and gastrointestinal complaints who received the MMR vaccine prior to the onset of ASD symptoms. The receipt of TCVs prior to the MMR vaccine was not a necessary condition for this theory, merely one that, according to petitioners, would enhance the likelihood that the measles virus could persist to trigger the onset of ASD in children genetically predisposed to the condition.

Ample reasons for the restricted nature of their theory exist. The most obvious one is that the MMR vaccine cannot cause autism in those in whom the condition manifested prior to the MMR vaccination. Thus, children with early onset or classic ASD were, by design, excluded from this particular theory.

It was the striking temporal connection between the MMR vaccination and the subsequent phenomenon of regression–the dramatic loss of language and/or other skills–that formed the basis for petitioners' theory. In Dr. Kinsbourne's words, it is evidence that "something must have most likely happened to change the trajectory of development in such a radical way." Snyder Tr. at 479A-80A. Thus, the search for a theory to explain how the MMR vaccine could cause autistic regression ensued.

The existence of gastrointestinal symptoms provided: (1) a site for inflammation which could affect the brain, as well as the gut, through the spread of proinflammatory cytokines; (2) a site from which measles virus itself could spread to the brain;[391] and (3) a site where measles virus could be detected more easily than directly in the brain. If inflammation, rather than direct invasion of the brain by measles virus, were the causal

[391] Petitioners' theories were somewhat unclear regarding a direct effect of the measles virus on the brain. Doctor Kinsbourne posited inflammation as a link in the causal process without directly stating that the inflammation must be caused by the measles virus itself in the brain. Snyder Tr. at 488A-89A; Cedillo Tr. at 1151-53, The presence of ILNH provided, at least in theory, a reservoir for measles virus which could then infect the brain.

mechanism, the virus might not be in the brain at all; detection in the gut could be sufficient to link ASD and ILNH to the same cause.

However, the problems with the case presented by petitioners for general causation are overwhelming. The quality of the petitioners' experts paled in comparison to the world-class experts proffered by respondent. The theories petitioners' experts advanced lacked support in both logic and research. As Dr. Ward testified, an hypothesis has a life span. An hypothesis may be biologically plausible at the time it is first advanced. As evidence accumulates, the hypothesis may be strengthened or weakened. The MMR hypothesis may have appeared biologically plausible at its inception, but the accumulating body of scientific evidence has tipped the scales decisively against it. Snyder Tr. at 975. The weight of the scientific evidence is that the measles vaccine virus plays no role in the pathogenesis or triggering of autism. I thus conclude that petitioners have failed to demonstrate that the MMR vaccine can cause autism, even in the highly circumscribed subset of children with regressive ASD and gastrointestinal symptoms.

Aside from the flaws evident in the theories of causation advanced, there are other reasons for concluding that MMR vaccine causation of autism is improbable. Without advancing an alternate cause, respondent produced compelling evidence that MMR causation of autism is unlikely, because epidemiologic studies have failed to detect any relationship between the MMR vaccine, TCVs, or the measles virus, and ASD. Evidence of the presence of measles virus genomic material in children with ASD is not reliable or persuasive as to causation because of faulty scientific methods and practices. The evidence for the postulated "separate phenotype" in ASD, that combines regressive autism and enterocolitis, is scanty and speculative. The occurrence of regression in temporal proximity to the MMR vaccine is insufficient, standing alone, to demonstrate a causal connection. Given that the MMR vaccine is administered to most children within the six to nine months before ASD symptoms become apparent, a temporal relationship between the vaccine and onset of symptoms would be likely in many, if not most, cases of ASD. *See Grant*, 956 F.2d at 1148 (a proximate temporal association alone is not sufficient to establish vaccine causation).

A. Credibility of Experts.

In courts that apply the Federal Rules of Evidence, it is doubtful that some of petitioners' expert witnesses would have withstood challenge under *Daubert* and Rule 702, based on their lack of qualifications to opine on the subjects at issue and the speculative and unsupported nature of their opinions. In cases filed under the Vaccine Act, where the rules of evidence do not apply, *Daubert* does not generally serve as a basis to exclude testimony, but rather, a framework to weigh and evaluate testimony. As Justice Blackmun said in *Daubert*:

> But, in order to qualify as "scientific knowledge," an inference or assertion must be derived by the scientific method. Proposed testimony must be supported by appropriate validation–i.e., "good grounds," based on what

> is known. In short, the requirement that an expert's testimony pertain to "scientific knowledge" establishes a standard of evidentiary reliability.

509 U.S. at 590.

Daubert provided a non-exhaustive list of factors for a court to consider in evaluating a proffer of expert testimony: (1) whether a theory has or can be tested; (2) whether the theory has been subjected to peer review and publication (a relevant, but not dispositive consideration); (3) the known or potential error rate of a technique; and (4) whether the theory enjoys general acceptance in the relevant scientific community. 509 U.S. at 593-94. *Kumho Tire* added that a trial judge must ensure "that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." 526 U.S. at 152. Justice Breyer added that, in applying *Daubert:*

> The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability, and to decide whether or when special briefing or other proceedings are needed to investigate reliability, as it enjoys when it decides *whether or not* that expert's relevant testimony is reliable.

526 U.S. at 152 (emphasis original).

The Ninth Circuit's *Daubert* decision after remand is particularly instructive to trial courts in evaluating proffered scientific testimony for adequate indicia of reliability. It offers many parallels to Vaccine Act cases in general, and the Theory 1 general causation testimony in particular. Like the Federal Circuit in *Althen*, the Ninth Circuit noted that causation can be established, even when the precise mechanism of injury is unknown, "if there is sufficiently compelling proof that the agent must have caused the damage *somehow.*" 43 F.3d at 1314 (emphasis original). The experts proffered by plaintiffs in *Daubert* fell into three categories: (1) those who reanalyzed studies showing no statistical association between Bendectin use in pregnancy and birth defects to demonstrate the existence of such a link; (2) those who relied on animal studies to demonstrate Bendectin causes birth defects; and (3) those who pointed to chemical similarities between Bendectin and other drugs suspected of causing birth defects. The circuit court noted that the "small but determined group of scientists testifying on behalf of the Bendectin plaintiffs" constituted the whole of a distinct minority of the scientific community. *Id.* The court also noted that the question of admissibility of an opinion arises only if it is first established that the proffered witness is in fact an expert in the relevant scientific field. 43 F.3d at 1315. A "self-serving assertion" by an expert that "his conclusions were 'derived by the scientific method'" is not binding on a court. 43 F.3d at 1316. The party offering that expert "must show that the expert's findings are based on sound science, and this will require some objective, independent validation of the expert's methodology." *Id.*

The Ninth Circuit applied an additional factor to the analysis of an expert's opinion, one that is similar to the same intellectual rigor test the Supreme Court applied later in *Kumho Tire*. The circuit court considered whether the matters the expert proposed to testify about flowed from research conducted independently of involvement in the litigation in question, because this factor provides objective proof that the research was conducted for scientific purposes. 43 F.3d at 1317. *See also Exxon Shipping Company v. Grant Baker*, 128 S. Ct. 2605, 2626 n.17 (2008) (declining to consider research funded in part by a party to the litigation).

In this case, the question is not one of admissibility, it is one of weight, because in our bench hearings, there is no jury to be misled. For many of the reasons the Ninth Circuit on remand affirmed the district court's grant of summary judgment to the defendants, I conclude that the evidence advanced by petitioners in the Theory 1 general causation case does not establish causation by a preponderance of the evidence.

I find it significant that petitioners did not have a measles virologist to establish the biologic plausibility of their theory of measles virus causation. Instead, they offered the testimony of Dr. Kennedy, a well-respected virologist, but not one whose research had focused on measles. His only published work on the measles virus was a literature survey, written when he was an expert witness in the U.K. MMR litigation. Much of his testimony in *Snyder* drew on an out-of-date verison of Dr. Griffin's chapter on measles virology, as he testified to matters omitted from the most recent version.

Petitioner's immunologist, Dr. Byers, is not board certified in allergy and immunology, does not see patients outside of a litigation context, has no expertise in mercury's impact on the immune system, and offered opinions on immune system testing (the use of adult parameters to measure adequacy of immune function in children) that defied logic, common sense, and were counter to the published, peer reviewed medical literature.

Doctor Kinsbourne, although otherwise a well-qualified pediatric neurologist, has conducted no research on autism, has not actively treated patients for more than 17 years, has published only a few speculative and theoretical articles on autism, plus one textbook chapter dealing with developmental disorders, changed a chart on autism's known causes in one of his book chapters to create the impression that measles is a recognized cause of autism, and whose more recent place of work appears to be the courtroom, not the laboratory. He advanced theories that are based on testing at a laboratory with known error rates that are unacceptably high and results that are scientifically implausible, are unsupported by the weight of the scientific literature, and which fly in the face of what is known about the measles virus and central nervous system infections.

Doctor Corbier fares little better. Evaluating his testimony in a general causation context only (not considering his opinions on Yates Hazlehurst as a treating physician), Dr. Corbier's testimony is personal opinion, not science. *See Turpin v. Merrell Dow*

Pharmaceuticals, Inc., 959 F.2d 1349, 1360 (6th Cir. 1992). He has conducted no personal research into autism's causes, and the research upon which he relied was not, in general, supportive of his position on either measles or autoimmunity as a cause.

Doctor Hepner was well-acquainted with how to perform PCR, but nothing in her background or publications reflected any expertise in detecting measles virus in tissue or body fluids. Her only research into measles virus detection had not been published, much less subjected to peer review. Yet, she proffered favorable opinions on the quality of the testing described in the Uhlmann paper, without any knowledge of Unigenetics' actual error rate. She failed to rebut the findings of Dr. Ward's laboratory demonstrating that the F gene primers used by Unigenetics amplified host tissue as well as the measles virus.

Doctor Krigsman was qualified to testify about gastroenterology. However, his testimony was not enhanced by his professional difficulties. His qualifications to establish the validity of a new form of gastrointestinal disorder, unrecognized by other authorities in the field, were, even when inflated, sadly lacking.

Doctor Aposhian was well-qualified to discuss mercury toxicology in general, but his penchant for conflating the species of mercury when discussing toxicity did not enhance his credibility. His testimony appeared similar to the disqualified experts in *Daubert,* who were willing to testify that Bendectin caused birth defects, based on similarities in chemical structure, rather than specific research. In any event, his testimony became peripheral to the central issue of MMR causation in these cases, as he did not link TCVs to immune dysfunction or suppression, and Dr. Byers was ineffective in her attempts to do so.

B. The Failure of Proof.

1. There is No Evidence Wild-Type Measles Virus Causes ASD.

Leaving aside the *Daubert* analysis of petitioners' experts' qualifications and opinions, other evidentiary problems are glaringly apparent. One obvious and overwhelming problem with the PSC's first theory of vaccine causation is that there is virtually no evidence that the wild-type measles virus can cause ASD, either directly, through some action of the pathogen on the brain, or indirectly, by creation of a disease or symptoms, such as inflammation, that triggers the onset of ASD. The Vaccine Program has long recognized that if a pathogen can cause a particular disease or side effect of a disease, it is likely that the vaccine against that pathogen can do so as well, a position endorsed by respondent's experts, Drs. Ward and Griffin with regard to the measles virus. *See also* K. Stratton, *et al.*,eds. Vaccine Safety Committee, Institute of Medicine, *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (1994) at 22 ("the vaccine-adverse event association should be plausible and coherent with current knowledge about the biology of the vaccine and the adverse event. Such information includes experience with the naturally occurring infection against which the vaccine is given, particularly if the vaccine is a live attenuated virus.").

If the pathogen itself cannot cause the condition, it is unlikely that the vaccine against the pathogen can do so, absent an autoimmune reaction to the vaccine or a component thereof.[392]

No evidence was introduced that suggests that congenital measles, unlike rubella, is related to the development of ASD. Likewise, there was no reliable evidence that post-natal measles infections can cause ASD. Although Dr. Kinsbourne testified about a 1948 case report[393] that purportedly linked measles disease to autism, I did not find his testimony supported by the article. Doctor Ward reviewed a translation of the abstract of the Bosch case report, and testified that the article concerned two cases of "infantile dementia" with onset shortly after a natural measles infection. Cedillo Tr. at 1825A-28A.

Calculating that between 1948 and 1978, when the measles vaccine became widely available, approximately nine billion children were born, Dr. Ward testified that virtually all of these children would have been infected with wild-type measles, most before they were three years old. Between 1948 and 1978, there were no other case reports of an association between measles disease and autism, much less any studies linking measles to ASD. Cedillo Tr. at 1826A-28A.

Thus, Dr. Kinsbourne's use of the Bosch article as support for biologic plausibility of measles virus causation is extremely weak. Not only is it far from clear that the "infantile dementia" described was a condition consistent with an ASD diagnosis, the lack of any other report of an association between measles disease and autism makes the connection extremely improbable.

Adding to this improbability are several epidemiologic studies that attempted to find a relationship between measles virus and ASD. No relationship was detected.[394]

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[392] Adjuvants or contaminants in a vaccine could, theoretically, trigger an adverse vaccine reaction, but that is not the theory advanced in the Theory 1 cases. The Theory 2 cases presented the evidence that the thimerosal component of vaccines can cause ASD.

[393] V. Bosch, *Demenz als Folge von Masern-Encephalitis im Kleinkindersalter,* DER NERVENARZT 19: 254-64 (1948) ["Bosch"], filed (in German) as Cedillo Pet. Ex. 61, Tab QQQ. As this is apparently the only article suggesting that wild-type measles could cause autism, it is inexplicable that petitioners, whose expert apparently considered this theory plausible, did not file a translated copy.

[394] *See, e.g.,* W. Chen, *et al., No evidence for links between autism, MMR and measles virus*. J. PSYCHOL. MED. 34: 543-53 (2004) ["Chen"], filed as Cedillo Res. Ex. P, Tab 28. The Chen study (which Dr. Fombonne co-authored) used the U.K. National Autistic Society membership to identify 2407 autistic individuals born between 1959-1993. The study examined prenatal and post-natal exposures up to the age of 18 months to wild-type measles virus, the monovalent measles vaccine, and the MMR vaccine. Prior to 1967, no measles vaccine was available and any exposure would have been to the wild-type measles virus. From 1968 to 1986, the primary exposure was to the monovalent measles vaccine; from 1987 to 1991, to the MMR vaccine, and from 1991 to 1993, to a modified MMR vaccine. No associations between measles outbreaks or epidemics and rates of autism were observed. *See* discussion of this study at Cedillo Tr. at 2548-51A. Additional studies are discussed below.

In spite of the existence of measles vaccines, approximately 500,000 children a year worldwide still experience wild-type measles infections. Despite the widespread nature of such infections, and the growing awareness of autism as a disorder even in the developing world, the medical literature still contains no reports of any association between wild-type measles and autism. This is not an association that would be missed because measles outbreaks come in waves. The east coast of the U.S. and the eastern provinces of Canada had a measles outbreak in the 1990s, with thousands of cases reported. There was no sudden spike in the number of autism cases in either locale after these measles outbreaks. Snyder Tr. at 949A.

Assuming, *arguendo*, that measles virus directly causes autism, petitioners did not proffer any explanation for why the rates of autism were apparently much lower when measles disease was epidemic or endemic.[395] A child in 1950 who displayed some disorders on the autism spectrum would likely have been diagnosed as mentally retarded or suffering from a childhood psychosis, rather than as autistic. However, it seems highly unlikely that a connection would have been missed entirely between measles disease and such behaviors. To the extent that petitioners are contending that TCV exposure was necessary to set the stage for susceptibility to the measles vaccine, they have overlooked the other sources of mercury then present in over-the-counter medications, such as teething powders or merthiolate, during the period before the development of new vaccines and concomitant increased TCV exposure.

The wild-type measles virus causes measles disease and its accompanying fever, rash, and other symptoms. It can also cause SSPE, MIBE in immunocompromised individuals, and is one of the many possible triggers for the autoimmune disease PIEM. The two persistent measles viral infections, MIBE and SSPE, involve mutations of the virus, obvious pathologic changes in the brain, and a relentless neurologic deterioration resulting in death.[396] These conditions are not similar to ASD, either in symptomatology or prognosis. When measles virus directly infects the central nervous system, there is a persistent and progressive impairment of the level of consciousness. In ASD, there are declines, improvements, and plateaus.

The wild-type measles virus can also indirectly cause, or contribute to, a wide variety of conditions. Worldwide, pneumonia and diarrhea, caused by opportunistic infections after measles disease, still kill thousands of children annually. Clearly, measles disease can cause fever and inflammation. Yet those parts of the world where measles disease is still a major threat to public health do not appear to have rates of

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[395] The initial results of two major surveys of ASD in the U.S. were released in February, 2007. The prevalence estimates for eight-year-olds in 2000 was 6.7 per 1000 (67 per 10,000). The prevalence rate was measured again in eight-year-olds from the same states in 2002. The average figure was 6.6 per 1000 (66 per 10,000), indicating that between 2000 and 2002, the prevalence rate was essentially unchanged. However, these rates reflect a marked increase in autism diagnoses from the 4-5 per 100,000 rate estimates in 1960s and 70s. Cedillo Tr. at 2510-12; Cedillo Res. Tr. Ex. 21 at 5.

[396] *See* Chapter 44, FIELDS VIROLOGY, Cedillo Res. Ex. R, Tab 18, at 1424.

ASD in excess of those in the Western world.

2. Epidemiology has Failed to Detect any Association between the MMR Vaccine and ASD or Co-Morbid Gastrointestinal Complaints.

Could ASD be caused by the vaccine strain virus, but not the wild-type virus? This is, in essence, the MINE theory proposed in Dr. Dyken's editorial and mentioned, in passing, by Dr. Kinsbourne. If it could, the introduction of the measles vaccine should have triggered a sudden spike in the cases of ASD in the period following the introduction of the vaccine. However, a number of well-conducted epidemiologic studies have found no such increase.[397]

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[397] *See* B. Taylor, *et al., Autism and measles, mumps, and rubella vaccine: No epidemiological evidence for a causal association,* LANCET 353: 2026 (1999) ["Taylor 1999"], filed as Cedillo Res. Ex. P, Tab 145; DeStefano, Cedillo Res. Ex. P, Tab 38; K. Madsen, *et al., A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism*, NEJM 347(19): 1477 (2002) [Madsen"], filed as Cedillo Res. Ex. P, Tab 105; L. Smeeth, *et al., MMR vaccination and pervasive developmental disorders: a case-control study*, LANCET 364: 963-69 (2004) ["Smeeth"], filed as Cedillo Res. Ex. P, Tab 137; and L. Dales, *et al., Time Trends in Autism and in MMR Immunization Coverage in California*, JAMA 285(9): 1183-85 (2001) ["Dales"], filed as Cedillo Res. Ex. P, Tab 33.

The Taylor 1999 study was a time trend analysis to determine if there was an increased incidence of autism diagnoses after 1988, when the MMR vaccine was introduced in the U.K. An examination of the records of over 400 children with ASD, born between 1979-1992, found that the number of cases by year of birth increased steadily, without any sudden increase after introduction of the MMR vaccine.

The DeStefano study, a 2004 case-control study based in metropolitan Atlanta, compared the age at the first MMR vaccination between children with ASD and typically developing children. The study compared 624 children with ASD (including subgroups of children with and without regression) to 1824 control children, matched for age, gender, and school. The data demonstrated that similar proportions of case and control children were vaccinated by 18 months and before 24 months.

The Masden study was a very large retrospective cohort examination of records for all children born in Denmark from 1991-1998, 82% of whom received an MMR vaccination. It found no association between vaccination, or age at vaccination, and the development of an autistic disorder. Doctor Fombonne described this as a very powerful and important study because of its design, nationwide scope, and extremely high statistical power. Cedillo Tr. at 2539A-41A.

The Smeeth study was a large case-control study based on the U.K. General Practice Research Database. It compared 1294 children with ASD to 4469 controls, matched for age, gender, and primary care providers. It found no connection between MMR vaccination and autism. The Smeeth investigators also included a meta-analysis of the Madsen and DeStefano studies, along with the data generated from their own study. All of the studies showed a relative risk of less than one. Combined, the odds ratio was 0.87, with a confidence interval of 0.76-1.001. Cedillo Tr. at 2541A-45A; Cedillo Res. Tr. Ex. 21 at 21 (reproduction of chart contained in the Smeeth study).

The Dales study was an ecological study of trends in diagnosis of autism in California between 1980-94. Filed as Cedillo Res. Ex. P, Tab 33, it compared MMR vaccination rates in birth cohorts by 17 and 24 months of age, with the number of children in those birth cohorts diagnosed with autism. The relative increase in MMR vaccinations was 14%. In contrast, the relative increase in autism rates per births was 373% over the same period. *Id.* at 1184-85. The difference between the two trends suggests there is no relationship between them. Cedillo Tr. at 2553A.

Even if regressive ASD is the only type of ASD capable of being caused by the measles vaccine, some observable increase in the number of children with regressive autism after the introduction of the vaccine should be demonstrated in epidemiologic data. Clearly, regression occurred before the vaccine was introduced; in his 1943 article, Kanner described regression in several of his cases. Other researchers described the phenomenon in 1964.[398] Several researchers have attempted to quantify the percentage of autistic children who demonstrated regression before the introduction of the vaccine, finding percentages ranging from 25-40%, figures that track with the current estimates of regression at about 20%. Cedillo Tr. at 2563-64A.

Some studies have attempted to determine if the rate of regressive autism has increased over time. A 2002 time-trend study by Taylor[399] examined the rate of regression in 473 children born during the period from 1979-1998 to determine if the rate of regression changed upon introduction of the MMR vaccine in the U.K. The study found no significant difference in the rates of regression during this 20 year period. Cedillo Res. Ex. P, Tab 146, at 394; Cedillo Tr. at 2565A-66A.

A study in Japan[400] also looked at the postulated regressive autism phenotype, with similar findings. Because the MMR vaccine was only used in Japan from 1989-1993, the study looked at three periods: (1) prior to the introduction of MMR; (2) during its use; and (3) after its withdrawal from the market. This study had both a case-control component and a time-trend analysis component, providing, in the authors' words, "a double test of the MMR hypothesis." Cedillo Res. Ex. P, Tab 149, at 211. The study found that the rate of regression did not increase during the period in which MMR vaccinations were given, and, within that period, the rate of regression was not higher in children who received the vaccine than in those who did not. *Id.* at 214; Cedillo Tr. at 2566A-67. Potential biases in this study were that the samples were drawn from patients at a private clinic and that the sample size of children who received the MMR vaccine was small. Also, the study used parental reports of regression at the time of enrollment in the clinic to classify children for study purposes, which may have tended to overestimate the number of patients (38%) classified with regression. *Id*. at 215-16.

Doctor Fombonne also testified about his 2001 article (Cedillo Res. Ex. P, Tab 60) with regard to the postulated MMR-regressive autism link. A comparison of rates of regressive autism found before and after the MMR vaccine was introduced in the U.K. found no increase in the percentage of children with possible or definite regression. Cedillo Tr. at 2571A-72.

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[398] S. Wolff and S. Chess, *A Behavioural Study of Schizophrenic Children*, Acta. Psychiatr. Scand. 40: 438-66 (1964), filed as Cedillo Res. Ex. P, Tab 157.

[399] Taylor 2002, Cedillo Res. Ex. P, Tab 146.

[400] T. Uchiyama, *et al., MMR-vaccine and Regression in Autism Spectrum Disorders: Negative Results Presented from Japan*, J. AUTISM DEV. DISORD. 37(2): 210-17 (2007), filed as Cedillo Res. Ex. P, Tab 149.

Another study in Japan found similar results.[401] The Honda study examined the effect of the withdrawal of the Japanese MMR vaccine[402] on autism rates in Japan. The study broke the case children into three categories: without regression; probable regression; and definite regression. *Id*. at 575-77. The cumulative incidence of autism by age seven was determined for birth cohorts from 1988-1996. *Id*. at 574. The cumulative incidence of ASD rose from 47.6 per 10,000 for children born in 1988 to 117.2 per 10,000 for those born in 1996. The rate continued to rise in birth cohorts after 1996. There was no decline in ASD incidence during the years in which the MMR vaccine was not given. *Id*. at 576. Because the autism rates in Japan during the period when the MMR vaccine was not administered were at least as high as in other countries where the vaccine was in use, the authors concluded that MMR was unlikely to cause a substantial proportion of autism cases. *Id*. at 578. The study contained no information on exposure to TCVs. Cedillo Tr. at 2654-55A.

Petitioners characterized the co-occurrence of regressive ASD and gastrointestinal disturbances as "autistic enterocolitis," a separate phenotype of ASD and argued that the two conditions had a common cause–persistent measles virus. However, epidemiologic studies demonstrate that children with early onset or classic ASD have similar rates and types of gastrointestinal disorders as children with regression, and that children without ASD also have gastrointestinal symptoms with similar frequency.

A U.K. nested case-control study in 2002[403] found no significant differences in onset of gastrointestinal disorders in children with autism as compared with typically developing controls. It also found no temporal association between the onset of gastrointestinal symptoms and the MMR vaccine. The study did not, however, distinguish between autistic children with regression and those without. Cedillo Res. Ex. P, Tab 12, at 421.

A U.S. study[404] examined the frequency of gastrointestinal symptoms in children with autism by reviewing medical records, finding that 24% of such children had gastrointestinal complaints. It found that regression was not significantly associated

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[401] H. Honda, *et al., No effect of MMR withdrawal on the incidence of autism: a total population study*, J. CHILD PSYCHOL. PSYCHIATRY 46(6): 572-79 (2005) ["Honda"], filed as Cedillo Res. Ex. P, Tab 87.

[402] The vaccine was withdrawn based on problems with the mumps component, which was a different strain than the mumps vaccine included in the U.S. MMR vaccine. Cedillo Res. Ex. P, Tab 87, at 572.

[403] C. Black, *et al., Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database,* B.M.J. 325: 419-21 (2002), filed as Cedillo Res. Ex. P, Tab 12.

[404] C. Molloy and P. Manning-Courtney, *Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders,* AUTISM 7(2): 165-71 (2003), filed as Cedillo Res. Ex. P, Tab 112.

with gastrointestinal symptoms.

Doctor Fombonne testified about his own study,[405] which examined the possible association between regression and gastrointestinal symptoms. Such symptoms were reported in approximately 19% of children, with no association found. Cedillo Tr. at 2571A-73; Cedillo Res. Ex. P, Tab 60, at 7. His findings were confirmed in a 2006 study by Richler[406] that used a larger sample and a more specific definition of regression involving word loss or other skills.[407] There were no significant differences between the regressed and non-regressed groups in the rates of gastrointestinal disorders,[408] but there were significant increases in gastrointestinal symptoms in the regressed group. Cedillo Tr. at 2573-74; Cedillo Res. Ex. P, Tab 124, at 11-12.

In Vaccine Act cases, the law is clear that petitioners cannot be required to produce epidemiologic studies to support a causation claim. *See Capizzano*, 440 F.3d at 1325. However, *Capizzano* does not prohibit respondent from introducing epidemiology to demonstrate that vaccine causation is unlikely. Epidemiology can never be direct proof that vaccines do not cause ASD, but it can be strong circumstantial evidence that causation is improbable.

Epidemiologic evidence certainly has limitations. An epidemiologic study cannot speak to causation in an individual case. It can, however, sufficiently undermine a hypothesis or theory regarding causation, making reliance on such a theory unreasonable under all the facts and circumstances of an individual case.

As Dr. Kinsbourne testified, epidemiologic studies identify associations between events, pointing the way for further scientific studies to determine whether the associations are causal or coincidental. Cedillo Tr. at 1058A-60. In science and medicine, epidemiology identifies target-rich environments–the best places to concentrate scarce resources for further study. To use *Althen's* terms, epidemiologic studies point out possible connections between two events; further scientific effort must ensue to establish whether the connections are biologically plausible and logical.

Each epidemiologic study filed has flaws that undoubtedly affect the data acquired and the conclusions drawn. However, when numerous studies have looked at

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[405] Fombonne and Chakrabarti 2001, Cedillo Res. Ex. P, Tab 60.

[406] Richler 2006, Cedillo Res. Ex. DD, Tab 12.

[407] A child was placed in the word loss group if the child had spontaneously used at least three meaningful words, other than "mama" or "dada," on a daily basis for at least one month, then stopped using all words for at least one month, prior to 36 months of age. Children without word loss, but who had lost at least 25% of skills in three or more skills areas, were also part of the "regression" category. Cedillo Res. Ex. P, Tab 124, at 4-5.

[408] The authors indicated that gastrointestinal disorders included Crohn's disease, colitis, and irritable bowel syndrome, among others. Cedillo Res. Ex. P, Tab 124, at 11.

a particular issue with the same or similar negative conclusions, the likelihood that the flaws have caused the negative results becomes vanishingly small. By analogy, one person searching his apartment for his cell phone might overlook it. When four or five searchers look through the apartment at various times, but still fail to find the cell phone, the likelihood that the cell phone is there becomes smaller. Some searchers may focus on the living room sofa; others may focus on the dining room or bedroom. Some may search more carefully and diligently than others, but each searcher contributes to the growing certainty of the conclusion that the cell phone is not there. The possibility remains, but the likelihood that it is present but undiscovered, declines with each successive search. Similarly, although epidemiology cannot establish that vaccines do not cause autism, it can establish the improbability that they do.

In searching for connections between ASD and various environmental factors, epidemiology has not stripped the apartment entirely bare. No epidemiologic study has examined whether a combination of TCVs and MMR is associated with autism, although studies have examined this possibility with both TCVs and MMR separately. There are no studies that have looked specifically at the causes of regressive autism, as opposed to autism in general. There are, however, studies that have explored an association between regressive autism and MMR, with no association found. Additionally, no studies have looked specifically at regressive autism in children with gut inflammation. Cedillo Tr. at 1058-60; 2679A-80A. These "unsearched" areas leave open the very slim possibility that an association exists. However, the nature and number of the studies already conducted makes the possibility highly remote.

Researchers have not ignored the striking temporal connection between the MMR vaccination and the onset of regressive autism. When the connection has been examined more closely, the temporal relationship becomes less striking. The MMR vaccination has been routinely administered to children between 12-18 months of age, with coverage rates of 80-95%. Thus, the vast majority of children with regression would have received the MMR vaccine in the months immediately prior to the age at which parents first become concerned about their child's development and when a loss of skills is most likely to have been noted. Causally linking the two events would require a showing that more children with regression had received the MMR vaccine than either children without ASD or with an ASD but no regression. Alternatively, a causal connection might be demonstrated by evidence linking a particular time frame after vaccination in which regression would likely occur. Two studies attempted to do just that.

The DeWilde study[409] looked at the U.K. general practice database for evidence of an increase in health care provider visits post-MMR vaccination. They found records for 71 children with a diagnosis of autism and receipt of MMR before diagnosis, and

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[409] S. DeWilde, *et al., Do children who become autistic consult more often after MMR vaccination?* BRITISH. J. GEN. PRACT. 51: 226-27 (2001), filed as Cedillo Res. Ex. P, Tab 40. By "consult" the authors meant visits to a physician.

matched each of them to four controls based on age, gender, month of MMR vaccination, and health care provider. The study looked at the number of consultations for each child with his or her primary care providers in the six months before and after the MMR vaccination. It found no significant difference in the number of such consultations, in either the two-month window or the six-month window before or after the MMR vaccination. Cedillo Tr. at 2546A-48.

However, in the six months prior to the diagnosis of autism, the number of patient contacts with the primary care team was higher for the case children than the controls. As the median time between MMR vaccination and autism diagnosis was 1053 days, there was no overlap between the six months after the vaccination and the six-month window before diagnosis. Cedillo Res. Ex. P, Tab 40, at 227; Cedillo Tr. at 2547A-48. The study casts considerable doubt on the validity of parental reports of connection between MMR and the first behavioral manifestations of autism.

Doctor Fombonne also testified about one of his own studies[410] examining the ages of autistic children when parents first noted developmental concerns. The mean age at which parents became concerned did not materially vary, regardless of whether the children had received an MMR vaccine. If the vaccine triggered onset, the data should have demonstrated an age shift closer in time to the date of vaccination (mean age of 12.5 months) in the vaccinated children. Cedillo Tr. at 2570A-72.

Three different types of epidemiologic studies have examined the hypothesis that the MMR vaccine causes autism. Case-control studies and cohort studies have looked at individual children to assess whether MMR vaccination increased the risk of developing ASD. Ecological studies have examined rates of ASD in populations over time to determine if changes in vaccination policies have affected autism rates. Some studies have focused primarily on Dr. Wakefield's hypothesis of a separate autistic enterocolitis phenotype. Cedillo Tr. at 2532-33. All of the reputable studies[411] have failed to find any statistical connection between ASD and the MMR vaccine.

3. Measles Virus Has Not Been Reliably Detected in Children with ASD.

The only evidence that truly distinguished children with "regressive autistic enterocolitis" from other children was the finding of measles virus in gut or CSF. Was this evidence sufficiently reliable to suggest that the virus was causal of ASD and/or gastrointestinal disorders? I conclude that it was not.

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[410] Fombonne and Chakrabarti 2001, Cedillo Res. Ex. P, Tab 60.

[411] Although several epidemiologic studies, primarily authored by Dr. and Mr. Geier, purported to find a relationship between vaccines and autism were filed, petitioners did not present any testimony about them. *See* n. 204, *supra.*

The bedrock of the scientific process is reproducibility.[412] If a result or effect is real, it can be repeated. If a different result obtains from efforts to duplicate it, the experiment must, at a minimum, be repeated. Cedillo Tr. at 2014-15A. Unigenetics' results could not be duplicated by any other researchers, with the possible exception of the incomplete study performed by Drs. Walker, Hepner, and Krigsman. The preliminary nature of that work precludes placing any significant reliance on it. Unless measles virus can be detected in greater numbers of children with ASD than in typically developing children, the preliminary findings are largely irrelevant in establishing a causal connection between measles genomic material and gastrointestinal complaints, much less a connection with ASD. The mere presence of measles virus in gut tissue would be extremely weak circumstantial evidence of MMR causation of autism, particularly in view of the paucity of evidence that "autistic enterocolitis" is a separate phenotype of autism. The presence of measles virus in CSF, if reliable, would present a different, and far stronger, case for causation, even if petitioners could not demonstrate such a finding more frequently in children with ASD than in their typically developing peers. Unfortunately, the evidence for the presence of measles virus in CSF is not reliable, because of the flaws in Unigenetics' testing.

C. Conclusion.

Doctor Rust used the term "scientific fraud" in describing the information upon which the MMR theory of causation is based. While noting that scientists are very careful about using that term, he testified that there was "abundant evidence" of scientific fraud in the body of evidence developed to support the MMR-autism hypothesis. Hazlehurst Tr. at 506A-07A. Sadly, the petitioners in this litigation have been the victims of bad science, conducted to support litigation rather than to advance medical and scientific understanding of ASD.

The evidence in support of petitioners' causal theory is weak, contradictory, and unpersuasive. This is particularly apparent when considering the impressive body of epidemiologic evidence contradicting their theories.

The "logical connection" between MMR vaccination and onset of regression was also undercut by a considerable body of evidence showing onset of regression can be triggered by gene expression. Children with Rett's disorder, which is entirely genetic in nature, evince loss of skills at specific times in their development, without triggering events. Other genetic conditions manifest when a particular gene is expressed; for example, Huntington's chorea manifests decades after conception, without a triggering event. Given the complex genetic basis for ASD and the epidemiologic investigations into regression, gene expression is a more likely explanation than the MMR vaccine for the manifestation of regressive ASD symptoms.

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[412] Interestingly, Dr. Wakefield's commentary in *Snyder* echoes the importance of reproducibility. In commenting on Dr. Singh's laboratory findings, Dr. Wakefield wrote: "The number of samples is not important at this stage. What is important is the reproducibility." Snyder Pet. Ex. 27 at 2.

Doctor Fombonne summed up the body of scientific research into ASD's causes and the petitioners' TCVs-MMR vaccine hypothesis, saying the possibility that some children are genetically predisposed to abnormal reactions to TCVs and the MMR vaccine so as to cause autism was less likely than the possibility of the earth being the center of the solar system. Cedillo Tr. at 1486A-88. His statement is an exaggeration of the evidence (or lack thereof), but is a concise and pithy expression of the general scientific disapproval of petitioners' theories.

The OAP began in 2003 with a plea by the PSC to "let the science develop." The science has developed in the intervening years, but not in the OAP petitioners' favor. The science will continue to develop, and, as science is not immutable, the parties in the OAP litigation remain free to supplement the evidence developed in the Theory 1 test cases with new evidence and new studies, as additional cases are presented for resolution.

The general causation evidence developed thus far will now be applied to evaluate the merits of Colten's specific claim for compensation.

Section VIII. Colten's Specific Causation Claim.

A. Introduction.

Most of the relevant procedural history pertaining to Colten's claim was discussed above and therefore will not be repeated here. The parties have stipulated that Colten's claim was timely filed and that his vaccinations were administered in the United States. Joint Submission of Issues Not in Dispute ["Jt. Submission"], ¶¶ 11-12, filed on October 26, 2007. All of the statutory prerequisites to entitlement have been established by stipulation or preponderant evidence, except that of causation. To prevail, petitioners must prove by preponderant evidence that Colten's condition, PDD-NOS,[413] was caused either by his MMR vaccine or by the thimerosal component of other vaccines acting in concert with the MMR vaccine.[414] The record as a whole fails

[413] Whether Colten still holds a PDD-NOS diagnosis is uncertain, but it is clear that the condition persisted longer than the statutorily required six months. He was released from the developmentally delayed category at school in August, 2004. Snyder Pet. Ex. 15, p. 125.

[414] The parties stipulated that thimerosal was present in "preservative amounts" in the three hepatitis B vaccines and the three hemophilus influenzae type b ["Hib"] vaccines Colten received prior to his MMR vaccine. Jt. Submission, ¶ 10. They have also stipulated that thimerosal was not present, or present only in trace amounts, in the diphtheria, tetanus, and acellular pertussis ["DTaP"] vaccination he received on July 9, 1998, two and one-half months after his MMR vaccination. *Id.*, ¶¶ 9-10. The records of the Hib vaccination Colten received concurrently with the MMR vaccination are insufficient to establish whether the Hib vaccine contained any thimerosal. *Id.*, ¶ 10. Neither the joint stipulation nor any evidence submitted at the hearing established the exact amount of thimerosal Colten received, although Dr. Bradstreet referred to "his 100 plus micrograms of mercury in the form of Thimerosal" without explaining how that figure was derived. Snyder Tr. at 285A. The MMR vaccine itself does not contain any thimerosal. *See* IOM 2004 Report, Cedillo Res. Ex. JJ, at 184.

to demonstrate that Colten's PDD-NOS was caused by his vaccinations.

B. Colten's Medical History.

1. Resolving Conflicts in the Evidence.

Colten's medical condition prior to and after his MMR vaccination on April 23, 1998, was established through his medical records, affidavits, videos, and testimony. Mrs. Snyder (Colten's mother) and Ms. Noonan (Colten's aunt) testified about Colten's condition throughout the period from his birth to the hearing. Ms. Kathy Timlin, Colten's former speech therapist, testified about her treatment of Colten during the period following his diagnosis through his discharge from speech therapy in 2003. Doctor Bradstreet testified as Colten's treating physician from July, 1999, through the time of the hearing. Although petitioners filed six expert reports authored by Dr. Bradstreet and several medical journal articles he authored or co-authored, he was specifically identified as a treating physician.[415] As Dr. Bradstreet did not begin treating Colten until July 28, 1998, some 15 months after his MMR vaccination, his assessments of Colten's condition prior to, or in the months after, his vaccination are based, like those of Drs. Ward and Wiznitzer, on the medical records and parental reports. However, I recognize that Dr. Bradstreet had close and continuing contact with Colten and his parents, and thus had access to more information than may be reflected in Colten's medical records.

The medical records and testimony, particularly regarding whether Colten exhibited behaviors suggestive of ASD prior to his MMR vaccination and what transpired after Colten's MMR vaccination, were sometimes conflicting. Conflicts between contemporaneous medical records and subsequent statements, testimony, and medical histories are common in Vaccine Act cases.

Two general legal principles guide the resolution of conflicts between contemporaneous records and later-adduced evidence. The first is that the absence of a reference to specific symptoms in a medical record does not conclusively establish the absence of symptoms during that time frame. *See, e.g., Murphy v. Sec'y, HHS*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. denied*, 506 U.S. 974 (1992) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance.")

The second principle addresses the degree of reliance commonly accorded to contemporaneous records. Special masters frequently accord more weight to contemporaneously recorded medical symptoms than those recounted in later medical histories, affidavits, or trial testimony. "It has generally been held that oral testimony

[415] Snyder Pet. Prehearing Memo at 4.

which is in conflict with contemporaneous documents is entitled to little evidentiary weight." *Murphy,* 23 Cl. Ct. at 733 (1991). *See also Cucuras v. Sec'y, HHS*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). Memories are generally better the closer in time to the occurrence reported and when the motivation for accurate explication of symptoms is more immediate. *Reusser v. Sec'y, HHS*, 28 Fed. Cl. 516, 523 (1993). Inconsistencies between testimony and contemporaneous records may be overcome by "clear, cogent, and consistent testimony" explaining the discrepancies. *Stevens v. Sec'y, HHS*, No. 90-221V, 1990 WL 608693, at *3 (Fed. Cl. Spec. Mstr., Dec. 21, 1990). *See also Burns v. Sec'y, HHS*, 3 F.3d 415, 417 (Fed. Cir. 1993) (decision to credit contemporaneous medical records over oral testimony "uniquely within the purview of the special master."). The following medical history and the conclusions drawn therefrom are presented with these legal principles in mind.

2. Prenatal and Birth Records.

Doctor Bradstreet described Colten's prenatal course as essentially normal. Snyder Tr. at 146A. At birth on January 9, 1997, Colten weighed seven pounds, three ounces, and had Apgar scores of nine at both one and five minutes.[416] Snyder Pet. Exs. 3, p. 2 and 6, p. 4. Colten received his first hepatitis B vaccine shortly before his hospital discharge on January 11, 1997. Snyder Pet. Exs. 5, p. 1 and 15, p. 11.

3. Medical Care and Treatment Prior to MMR Vaccination.

Mrs. Snyder and Ms. Noonan both described Colten's developmental progress as normal, until he received his MMR vaccination. Snyder Tr. at 41-43, 87. Doctor Bradstreet also testified that Colten's developmental progress was normal. Snyder Tr. at 146A, 154A-55. The medical records presented a slightly different picture, in that Colten showed an early sign of developmental delay followed by apparently normal development. The video records showed some behaviors that, at least in retrospect, reflect areas of concern. Additionally, the records and testimony are somewhat inconsistent regarding Colten's vocabulary and language development prior to his MMR vaccination.

Between Colten's discharge from the hospital after his birth and his two month well-baby visit, Colten had three medical visits to the Halifax Family Health Center ["HFHC"] for illnesses[417] and one trip to the Halifax Medical Center ["HMC"] emergency

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[416] The Apgar score is a numerical assessment of a newborn's condition, usually taken at one minute and five minutes after birth. The score is derived from the infant's heart rate, respiration, muscle tone, reflex irritability, and color, with from zero to two points awarded in each of the five categories. *See* DORLAND'S at 1670.

[417] He saw Dr. Thomas Land on January 27, 1997, for a non-productive cough. He was described as alert, smiling, and in no acute distress. He was recorded as breastfeeding. Snyder Pet. Ex. 7, p. 64. Colten was seen again February 3, 1997, for a recheck of his upper respiratory infection ["URI"] symptoms. His cough persisted and he had a clear, runny nose, which was worse at night. He had a

room. The March 2, 1997 emergency room visit was prompted by Colten's three week history of a cold and congestion without fever. After examination and a chest x-ray, he was diagnosed with upper respiratory congestion. His parents were told to return if he had fever or increased respiratory distress. Snyder Pet. Ex. 11, pp. 52-54.

His two month well-child checkup on March 12, 1997, was at the HFHC. His height and head circumference were at the 50th percentile and his weight was at the 75th percentile, coinciding with Mrs. Snyder's description of him as a chubby baby. He had a mild papular rash on his arms and face, a possible reaction to a new bath soap. He received his second hepatitis B vaccination, his first diphtheria, pertussis, and tetanus ["DPT"] and Hib vaccination[418] and his first oral polio vaccine at this visit. Snyder Pet. Exs. 7, p. 61 and 15, p. 11; Snyder Tr. at 39.

During the period between his two month and four month well-child checkups, Colten logged three visits to either the emergency room at HMC or to HFHC. All three visits concerned possible allergic reactions to formula after exclusive breastfeeding.[419]

On March 19, 1997, at the second of these three visits, Colten's temperature was 100.6, rectally. Doctor Land prescribed a ten-day course of an antibiotic. Snyder Pet. Ex. 7, pp. 59-60. On the third visit, on April 10, 1997, he saw Dr. Steven Sahai for the first time. Colten had a rash, emesis, and a discharge from his right eye that was diagnosed as an inflammation of the lacrimal gland in his eye. Snyder Pet. Ex. 8, p. 129.

At his four month well-child visit on May 9, 1997, Colten saw Dr. Sahai again. Snyder Pet. Ex. 8, p. 128. Colten received his second Tetramune and OPV vaccinations at this visit. Doctor Sahai recorded that Colten passed all of his developmental milestones, except rolling over.[420] He noted a little mild motor delay, and

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slightly elevated temperature, and his parents were advised to chart it and to return if it exceeded 100.4 degrees. At this visit, he was recorded as taking formula without problems. Snyder Pet. Ex. 7, p. 63. The February 6, 1997 visit was for emesis, and he was diagnosed with viral gastroenteritis. *Id*., p. 62.

[418] Colten received Tetramune vaccine, which contains both DPT and Hib. Snyder Pet. Ex. 7, p. 61.

[419] Colten had a severe rash on his face, ears, trunk, armpits, and groin at an emergency room visit on March 16, 1997. His parents reported that he had broken out with hives shortly after his first Enfamil formula feeding. He had problems with vomiting after a second type of formula was introduced, and refused to drink a third type of formula. Snyder Pet. Exs. 11, pp. 49-51, 7, pp. 59-60, and 8, p. 129. A history of exclusive breastfeeding, taken at the March 16, 1997 emergency room visit, conflicted with two prior entries in his medical records, which indicated he was taking formula. Snyder Pet. Ex. 7, p. 63 (reflecting formula feeding without problems) and Snyder Pet. Ex. 7, p. 62 (prescribing Pedialyte for a day followed by half-strength formula for a day or two for his gastroenteritis).

[420] Mrs. Snyder denied that Colten had any problems rolling over at four months of age. Snyder Tr. at 43. Given the other comments in Dr. Sahai's records concerning Colten's need for stimulation, I resolve this conflict in favor of the contemporaneous record.

indicated that Colten was not getting enough stimulation. Snyder Pet. Ex. 8, pp. 128. There were no other indications of any developmental delays in his records until after his MMR vaccination.[421]

In addition to well-baby visits on July 3[422] and October 1,[423] 1997, and on January 15, 1998,[424] Colten was treated for coughing, wheezing, otitis media, and pharyngitis. Snyder Pet. Ex. 8, pp. 113, 118, 120; Snyder Pet. Ex. 11, pp. 41-47. On May 12, 1997, three days after his four month well-child visit, he returned to Dr. Sahai's office with congestion and a mildly erythematous throat.[425] He was diagnosed with pharyngitis and treated with Amoxil for 10 days. Snyder Pet. Ex. 8, p. 127. On December 3, 1997, he was seen for cough, wheezing, and nasal congestion, and was diagnosed with bronchitis and allergic rhinitis. He was prescribed benadryl for the allergy, erythromycin for the bronchitis, and albuterol[426] for his wheezing. Snyder Pet. Ex. 8, p. 124. He returned again on December 23, 1997, with a history of vomiting off and on for about five days. He was diagnosed with viral gastroenteritis and prescribed Phenergan suppositories for the vomiting. Snyder Pet. Ex. 8, p. 123.

Between his first birthday on January 9, 1998, and his MMR vaccination on April 23, 1998, Colten was seen at an urgent care center for an ear infection on February 8;[427] at the HMC emergency room on March 1, for an exacerbation of reactive airway

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[421] At Colten's six, nine, twelve and fifteen month well baby visits, Dr. Sahai's records indicated that Colten was meeting all developmental milestones. Snyder Pet. Ex. 8, pp. 126, 125, 122, and 115.

[422] He received his third Tetramune and oral polio vaccinations at this visit. Snyder Pet. Ex. 8, p. 126.

[423] He received his third hepatitis B vaccination at this visit. His weight and head circumference were at the 45th percentile, while his height was at the 75th percentile. Snyder Pet. Ex. 8, p. 125.

[424] At his one year check up, Colten's height was at the 80th percentile, his weight at the 55th percentile, and his head circumference was at the 25th percentile. Snyder Pet. Ex. 8, p. 122.

[425] Erythematous means redness produced by capillary congestion. DORLAND'S at 638-39.

[426] Albuterol is a bronchodilator used to treat asthma. DORLAND'S at 45.

[427] At the Port Orange Urgent Care Center, Colten had a temperature of 101.6 degrees, with a nonproductive cough, runny nose, and decreased appetite, but no vomiting or diarrhea. His right tympanic membrane was erythematous. He was diagnosed with right otitis media and URI, and was prescribed a ten-day course of Amoxicillin for the ear infection and Tylenol for his fever. He was described as a well-developed and well nourished infant. His parents were told to follow up with his pediatrician in a week, but there is no record that they did so. Snyder Pet. Ex. 11, pp. 46-48.

disease;[428] at Dr. Sahai's office on March 19, for an exposure to streptococcus;[429] at the HMC emergency room on April 1, for falling and striking his head;[430] and at Dr. Sahai's office on April 7, 1998, for what was supposed to be Colten's 15 month well-child visit. Snyder Pet. Ex. 8, p. 118

During Colten's physical examination at the April 7, 1998 visit, Dr. Sahai discovered that Colten had enlarged tonsils with white patchy exudates on both. His eyes were mildly erythematous, with a conjunctival infection that appeared to be resolving. He had finished the course of amoxicillin prescribed on March 19, 1998. He was assessed as having a viral syndrome and pharyngitis, and prescribed symptomatic treatment. He was to return in 10 days for a well-child visit. Snyder Pet. Ex. 8, p. 118. Because a laboratory report on the pharyngeal sample taken at this visit showed a heavy growth of Escherichia coli ["E. coli. "] a type of bacteria normally found in the intestines,[431] a ten day course of Bactrim, an antibiotic, was prescribed. Snyder Pet. Ex. 8, p. 117.

In short, prior to his MMR vaccination, Colten had exhibited early signs of food allergies and asthma, in addition to a number of fevers and several gastrointestinal, respiratory, and throat infections.[432]

These medical records did not specifically reflect Colten's language development in terms of the number of words he used. Mrs. Snyder testified that his language development was normal, and that he used between 10-20 words prior to the vaccination, including a number of names of parents, siblings, and grandparents. She identified "car," "ball," and "bye bye" as other words he used. Snyder Pet. Ex. 33, p. 15; Snyder Tr. at 39, 43, and 80.

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[428] By report, Colten had been coughing and wheezing for 36 hours. Snyder Pet. Ex. 11, pp. 41-45.

[429] A sibling had the infection, but Colten's rapid strep test was negative. Colten was given Amoxil for ten days. At this visit, Dr. Sahai recorded that Mrs. Snyder was quite concerned about Colten because he was acting ill with low grade temperatures. He was diagnosed with strep-negative pharyngitis. Snyder Pet. Ex. 8, p. 120.

[430] Colten was described as neurologically "appropriate" at this visit. Snyder Pet. Ex. 11, pp. 39-40.

[431] *See* DORLAND'S at 642. Doctor Ward described E. coli as a "stool organism." Snyder Res. Ex. K, p. 2.

[432] According to Dr. McCusker, the average child has six to 10 infections per year between six months and two to three years of age. During this time period, the child's immune system is learning to recognize and fight infections and to generate immunological memory. That memory allows the body to recognize and fight subsequent infections by the same pathogen without clinically apparent illness. Hazlehurst Tr. at 568A. Doctor Bradstreet testified that Colten was immunologically normal prior to his MMR vaccination, as did Dr. Kinsbourne. Snyder Tr. at 256A, 493A-94A.

Videos of Colten taken between three weeks to 13 months of age were filed as Snyder Pet. Ex. 31.[433] Doctor Wiznitzer reviewed all the videos and identified several time periods as reflective of some developmental problems suggestive of ASD. The videos did not show Colten using language or sounds, other than screeches and one syllable sounds such as "ba" or "ma." There was no interpersonal babbling.[434] The videos showed siblings approaching Colten and talking to him, but, according to Dr. Wiznitzer, Colten did not talk back to them the way a baby would normally do. One video segment showed him, at about 7 months of age,[435] with another baby present who was babbling. Colten was silent. Snyder Tr. at 637A. He looked at the camera and played with the lens cover, but had inconsistent responses to voices. Sometimes he responded to his name, and sometimes he did not. To Dr. Wiznitzer, this raised a concern about Colten's use of language. Snyder Tr. at 638A. He testified that the family reports that Colten was using 15-20 words at 15 months of age reflected appropriate language development, if the words were being used for communicative purposes. Snyder Tr. at 666A. In Dr. Wiznitzer's opinion, based on the video evidence, Colten was not using words, merely syllables, at 13 months of age. Snyder Tr. at 667A.

According to Dr. Wiznitzer, there was not enough information in the videos to determine if Colten had deficits in social skills prior to his MMR vaccination. Snyder Tr. at 661A. Title 7 of the videos, taken when Colten was 11 months old, showed him being unresponsive to his name for a period of about 30 seconds. At Title 8 of the video, when he was thirteen months old, he was also unresponsive to his name. At Title 9, he was unresponsive to a hug. At Title 10, he was not looking at people, although he did go to his father. On Title 11, he was unresponsive to voice prompts and, on Title 13, he ignored his siblings. Although these videos were not definitive evidence of a lack of social skills, Dr. Wiznitzer called them suggestive of such a lack. Snyder Tr. at 661A-664A. There was no evidence on the pre-MMR vaccination videos of repetitive behavior. Snyder Tr. at 665A.

4. MMR Vaccination.

Colten returned to Dr. Sahai on April 23, 1998, for his 15 month well-child visit. He received his first MMR vaccine and his fourth Hib vaccine at this visit. Snyder Pet. Ex. 8, p. 115. Colten was described as appearing well. His height was at the 95th percentile, his weight at the 50th percentile (25 pounds, 14 ounces), and his head

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[433] The videos also included Colten from April, 1999, through slightly after his third birthday. There was a 13-14 month gap in the video record that Mrs. Snyder explained was the result of Colten's behavioral symptoms during this time period. The gap included the period from two months before his MMR vaccination to the beginning of his speech therapy, which was in April, 1999. Mrs. Snyder testified that she had neither the time nor the inclination to record his behavior during this period. Snyder Tr. at 71A.

[434] Titles 6-14 of Snyder Pet. Ex. 31; Snyder Tr. at 638A, 663A-64A.

[435] Title 6, Chapter 2, of Snyder Pet. Ex. 31; Snyder Tr. at 638A.

circumference at the 45th percentile. He had lost over one pound since his April 7, 1998, visit. *See* Snyder Pet. Ex. 8, pp. 118 (April 7, 1998) and 115 (April 23, 1998).

Commenting on the previous E. coli infection in his pharynx, Dr. Sahai recorded Mrs. Snyder as stating that Colten "does eat poop."[436] Snyder Pet. Ex. 8, p. 115. The throat culture taken at this visit did not show any bacterial growth (Snyder Pet. Ex. 8, p. 114). This was not surprising, in view of the antibiotics prescribed at the April 7, 1998 visit.

In the first notation of any language evaluation in Dr. Sahai's records, he commented that Colten had no signs of any receptive language disorders. He did not comment on Colten's expressive language skills or note any particular words or language being used by Colten prior to the vaccination. Snyder Pet. Ex. 8, p. 115. Doctor Sahai recommended a followup well-child visit in the next three months.

5. Medical Visits from MMR Vaccination to Hospitalization.

During the four to five weeks following his MMR vaccination, Colten had three visits to Dr. Sahai and two emergency room visits, all for problems similar to those he had previously experienced, including fevers, hives, general fussiness, and throat inflammation. *See generally*, Snyder Pet. Exs. 8, pp. 96-113 and 11, p. 38.

At trial, Mrs. Snyder's recollection of the same period was that, following the MMR vaccination, Colten "no longer slept. He would scream all night long." Snyder Tr. at 48A. According to Mrs. Snyder, Colten was fussy, inconsolable, suffering from fevers, no longer making eye contact, and that "he was just, he wasn't really there." Snyder Tr. at 48A-49A. He had profuse diarrhea after his MMR vaccination that never abated. Snyder Tr. at 56A. This change in behavior was what caused her to repeatedly bring Colten in to see the doctor. Snyder Tr. at 49-50. She also testified that the main reasons she took him to the doctor or the emergency room during this period were because of his extremely high fever and her inability to console him. Snyder Tr. at 76. Mrs. Noonan described Colten as a "different child" between his MMR vaccination and his hospitalization. Snyder Tr. at 92.

The medical records do not support Mrs. Snyder's characterization of the reasons for seeking medical attention for Colten. Fever and fussiness (crying and irritability) are the only complaints common to both Mrs. Snyder's testimony and the medical records between Colten's MMR vaccination and his hospitalization. At several points, the medical records affirmatively reflect that Colten did not have the symptoms that Mrs. Snyder testified that he demonstrated. For example, she described profuse

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[436] In testimony, Mrs. Snyder vehemently denied that Colten ever "ate poop." Snyder Tr. at 47A. I credit Dr. Sahai's records over Mrs. Snyder's testimony in this matter, not only because of the quotation in the medical records and the E. coli positive throat culture from the April 7, 1997 visit, but also because of a notation in Colten's records that Dr. Sahai had discussed "hygiene issues" with Mrs. Snyder "quite extensively" after the throat exudate tested positive for E. coli. Snyder Pet. Ex. 8, p.113.

diarrhea after his MMR vaccination (Snyder Tr. at 56A), but all the records from his visits up until the day of his hospitalization either record him as having no diarrhea or are silent. *See, e.g.,* Snyder Pet. Ex. 8, p. 113 ("no signs of vomiting, diarrhea or abdominal stress"). As Colten saw several different health care providers during this time frame, and none recorded sleep disturbances, screaming, lack of eye contact, or mental status changes (until the day of his hospitalization), it is unlikely that all of the health care providers were simply indifferent to Mrs. Snyder's reports. For these reasons, I rely primarily on the contemporaneous medical records for Colten's medical condition during this time frame.

I emphasize that I do not question Mrs. Snyder's veracity. She is a devoted and caring parent and I am confident that her testimony was based on her best recollection of this extremely difficult and stressful period in her life. For many years, Colten was a child who required considerable care, patience, and attention. Understandably, it appears that her histories of his illnesses have conflated some events. Occasionally, Mrs. Snyder's characterization of an event became part of a somewhat revisionist medical history, and was then relied upon by other doctors.[437] Thus, I rely primarily on the contemporaneous medical records for Colten's condition.

On May 6, 1998, 13 days after his MMR vaccination, Colten returned to Dr. Sahai. His mother reported that he was fussy and had increased crying, and decreased appetite. However, he was afebrile with no vomiting, diarrhea, or abdominal distress. On examination, Dr. Sahai found Colten's throat inflamed with erythema and "little white patchy exudates."[438] His strep screen was negative, and he was described as neurologically normal. Doctor Sahai injected Rocephin, an antibiotic, and asked that Colten return in 10 days for another throat swab. The record also contains the following notation: "Hygiene issues were discussed with mom quite extensively." Snyder Pet. Ex. 8, p. 113. The lab report for his throat swab showed normal flora. Snyder Pet. Ex. 8, p. 112.

The follow-up visit occurred on May 19, 1998, 26 days after his MMR vaccination and 13 days after his Rocephin injection. The history taken at this visit indicated that Colten had hives "about a week ago" after eating vanilla pudding with milk, and Dr.

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[437] For example, in the questionnaire she filled out for Dr. Bradstreet in May, 1999, she reported that in April, 1999, Colten became "completely out of control" in response to Augmentin, prescribed to him for cellulitis caused by an insect bite. Snyder Pet. Ex. 12, pp. 605, 643. Doctor Sahai did prescribe Augmentin, an antibiotic that Colten had previously taken without difficulty. Snyder Pet. Ex. 8, pp. 34, 60, and 77. Over the years, the adverse behavioral reaction became an "allergic reaction." *See* Snyder Pet. Ex. 12, p. 253 (describing Colten as allergic to penicillin) and Snyder Pet. Ex. 33, p. 2 (describing a penicillin allergy diagnosed by allergy testing). There are no records of any allergy testing for penicillin.

[438] During his testimony, Dr. Bradstreet speculated that these "patchy exudates" were actually Koplik's spots. Snyder Tr. at 156-57. This is unlikely, given Dr. Ward's testimony that Koplik's spots do not occur in response to the measles vaccine. Snyder Tr. at 833A. I also note that this was not the first time Colten experienced patchy exudates in his throat and tonsils. *See, e.g.,* Snyder Pet. Ex. 8, p. 118 (Colten's April 7, 1998 visit to Dr. Sahai, before his MMR vaccination).

Sahai noted that Colten seemed to have some milk intolerance. He had an eye discharge[439] and a few healing insect bites on his leg. Snyder Pet. Ex. 8. p. 111. Colten weighed 26 pounds, 2 ounces, at this visit, according to a later note by Dr. Sahai. *Id*., p. 92.

On Memorial Day weekend,[440] Colten's family attended a family picnic. Mrs. Snyder described Colten as just sitting on her lap. He did not play with his cousins and siblings. Snyder Tr. at 52A, 90. Mrs. Noonan described him as "unresponsive, totally lethargic, pale, thin." Snyder Tr. at 91. Colten visited the emergency room on May 24 and May 25, and was admitted to the hospital on May 26, 1998. Although Mrs. Snyder described the hospitalization as occurring before Memorial Day weekend (Snyder Tr. at 52A), the dates on the medical records clearly reflect that he was hospitalized on the day after Memorial Day, May 26, 1998.

Five days after last seeing Dr. Sahai (and 31 days after his MMR vaccination), on May 24, 1998, Colten was taken to Ormond Memorial Hospital's Emergency Room, with a history of fever of 104 degrees or higher for three days. His temperature at the emergency room was 101.1 degrees. He had a nonproductive cough and was fussy. He was given another Rocephin injection and prescribed Tylenol or ibuprofen for fever. He was also given a prescription for oral penicillin. The diagnosis was strep and right otitis media. Snyder Pet. Ex. 8, pp. 109-10.

Colten went to the HMC emergency room the next morning, May 25, 1998, with continuing fever and sore throat. His temperature remained high, ranging between 102 and 103 degrees. His appearance was "non-septic" but his tonsils had a white exudate bilaterally. His tympanic membranes were "ok." He appeared well-hydrated and neurologically intact. He was diagnosed with acute tonsillitis, to be treated with tepid baths, Tylenol, and increased fluid intake. Snyder Pet. Ex. 11, p. 38.

Doctor Bradstreet testified that Mrs. Snyder said Colten was sicker after his MMR vaccination than his medical records reflected. Snyder Tr. at 152A. Her own testimony was that she continually raised his health issues with his health care providers, but that her concerns fell on deaf ears. Snyder Tr. at 78A-79. However, Colten saw several health care providers, including Dr. Sahai, and none of them noted that any illness was significant, up to the point Dr. Sahai hospitalized him, discussed immediately below. Mrs. Snyder's testimony on this point is not sufficiently clear, cogent, or compelling to credit it over the contemporaneous medical records.

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[439] Doctor Sahai associated this conjunctivitis with Colten's pharyngitis and the allergic reaction to milk products a week earlier. Snyder Pet. Ex. 8, p. 111. Colten also had conjunctivitis with his April 7, 1998 pharyngitis. *Id*., p. 118.

[440] I judicially note that in 1998, Memorial Day fell on May 25th.

6. Colten's Hospitalization.

Doctor Sahai saw Colten on May 26, 1998, the day after his second emergency room visit, at his office. He noted a temperature of 102.6, and two emergency room visits over the last three days. In contrast to the Halifax ER records from the day before, which did not mention shaking, poor appetite, severe diarrhea, and some vomiting, all of these were reported by his parents as the symptoms prompting the emergency room visit. Given that he was described as "well-hydrated" at the HMC emergency room visit, and then dehydrated at Dr. Sahai's office, it is likely that at least the diarrhea and vomiting were relatively new symptoms, although Colten was clearly ill at both previous emergency room visits.

Doctor Sahai noted that Colten appeared limp, dry, and easily accessible, which was unusual. His anterior fontanel was described as "almost closed, sunken." Doctor Sahai also wrote that Colten was a "child with initially some mild motor delay, but has done quite well since...Colten appears flat lethargic, quiet, quite unnatural for him. He is normally a quite active child." Snyder Pet. Ex. 8, p. 99-100. He had mildly hyperactive bowel sounds, and his throat was inflamed with enlarged tonsils covered with white patchy exudates. Doctor Sahai planned to admit him to the hospital for IV hydration and antibiotics. Snyder Pet. Ex. 8, p. 96.

Doctor Sahai's notes upon Colten's admission to the Ormond Beach Hospital reported the two HMC emergency room visits in the prior two days. He identified fever, diarrhea, dehydration, gastroenteritis, and pharyngitis as the reasons for his admission. He expanded on his office notes, indicating that Colten looked "quite lethargic and ill" in the office, with "obvious mental-status type changes." He described a dehydrated child who was not producing tears. The parents gave a history of severe gastroenteritis-type illness with high fever. He repeated his observations of Colten's pharynx as inflamed and erythematous with bilateral white exudates. His lymph nodes were slightly enlarged bilaterally and his neck was supple. Doctor Sahai considered a possible viral illness or a return of the E. coli bacterial infection. He did not swab Colten's throat upon admission because Colten had received penicillin, which could cause a false negative throat culture. Snyder Pet. Ex. 8, pp. 97-98. Additionally, the admission questionnaire indicated that Colten had an abdominal rash upon admission. Snyder Pet. Ex. 10, pp. 30-31.

The nursing notes indicate that Colten was intermittently sleeping and irritable during his hospital stay. Although Mrs. Snyder later reported to Dr. Bradstreet (Snyder Pet. Ex. 12, p. 606) that Colten cried constantly and did not sleep during his hospitalization, and, in an interview with a social worker on January 12, 2000, she described him as screaming 23 hours out of 24 during this hospitalization (Snyder Pet.

Ex. 15, p. 204), the contemporaneous nursing notes contradict her descriptions.[441]

Laboratory tests taken during Colten's hospitalization yielded little helpful information concerning the specific cause of his illness. The blood culture had no growth; the feces culture was negative, with no parasites or ova found; and a test for rotavirus was negative.[442] Snyder Pet. Ex. 8, pp. 105-08.

However, the blood tests revealed leukocytosis and left shift. Snyder Pet. Ex. 8, pp. 101-02. Doctor Ward testified that the exudative pharyngitis and the elevated white count with a marked left shift were consistent with a bacterial infection. Most of the elevation of Colten's white blood cell count was caused by an elevated number of neutrophils, the white blood cells that respond to bacterial infections. In a left shift, the nucleus of the neutrophils has no lobes, appearing as a band, which means that the neutrophil is young. This elevated "bandamia" is indicative of an active bacterial infection. The laboratory data was not consistent with a viral infection because viral infections do not produce an elevated band count. Snyder Tr. at 972-73A. Colten's lymphocyte levels were too low for a viral infection and the small number (2-3%) of atypical lymphocytes present were not compatible with a viral process. Snyder Tr. at 971-74. Colten's lab results at the time of his hospitalization evidenced a functioning immune system. Snyder Tr. at 974-75.

The hospital records contained several comments on Colten's development. In his history, Dr. Sahai described Colten as a "child with initially some mild motor delay, but [he] has done quite well since. Occasional routine childhood illness." Snyder Pet. Ex. 8, p. 99-100. The developmental history assessment noted that Colten walked on his own, played with balls and toys, understood English, expressed himself, and had an appropriate level of understanding for his age. Snyder Pet. Ex. 10, pp. 30-31. The notes indicated that Colten was behaving in an age-appropriate manner.[443] *Id.* On

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[441] The nursing notes reflect that Colten slept from about 1400-1900 on the afternoon of his admission and was awake and crying or irritable from 2000-2300. Snyder Pet. Ex. 10, pp. 32, 34-35. The next day, May 27, 1998, Colten was half asleep at 0100, and slept from 0200-0400. He was awake and crying at 0400, and asleep from 0500-0800. He was alert from 0800-1600, fussy at 1700, resting at 1800, and alert at 1900. He was awake and irritable at 2000 and remained awake through 2300. Snyder Pet. Ex. 10, pp. 14-16. On May 28, 1998, the date he was discharged, Colten slept from 2400-0400, from 0500-0600, and from 0700-0900. He was awake and crying at 0400-0500 and awake from 0600-0700. Snyder Pet. Ex. 10, pp. 9-11. Mrs. Snyder's account to Dr. Bradstreet was given almost a year later, on May 11, 1999, when she stated that he had "Non-stop screaming/crying during hospital stay. Sleepless nights started." Snyder Pet. Ex. 12, pp. 641-42. Her recollection is at odds with the nursing notes, although it is clear that Colten was irritable during many of the hours he was awake.

[442] Rotavirus is a common cause of gastroenteritis in infants and children. DORLAND'S at 1643.

[443] According to Mrs. Snyder, by the time he was hospitalized, Colten had arrested his communication and was no longer playing with toys in a typical manner, instead favoring repetitive play. Snyder Tr. at 53A-54A. I adopt the accounts in the contemporaneous records, which reflect that Colten was still playing and communicating normally at the time of his hospitalization.

discharge, his neurological exam was normal, with no focal deficits. Snyder Pet. Ex. 8, pp. 101-02.

Colten was hospitalized on May 26, and discharged on May 28, 1998, spending less than 48 hours in the hospital. However, on Dr. Bradstreet's questionnaire, Mrs. Snyder indicated that Colten was hospitalized for four days, two weeks after his MMR vaccination. Snyder Pet. Ex. 12, p. 634. In a report to a social worker, Mrs. Snyder indicated that Colten was hospitalized for a week. Snyder Pet. Ex. 15, p. 204.

According to Dr. Bradstreet's testimony, Mrs Snyder told him that, at the time Colten was hospitalized, he had been ill for two weeks. Snyder Tr. at 159A-60. The contemporaneous records reflect approximately five days of fever prior to his hospitalization. If Colten were as ill as Mrs. Snyder implied for the two weeks immediately preceding his hospitalization, the records of at least one of the three health care providers he saw would surely have noted an illness of that duration.

Doctor Kinsbourne characterized Colton's lethargy prior to his hospitalization as the beginning of the social withdrawal that is part of autism's core features. Snyder Tr. at 528A-29B. Doctor Wiznitzer disagreed, testifying that the term "lethargy" had a particular clinical meaning, a mild diminution or decrease in level of consciousness, which is very different from the social withdrawal seen in autism. Snyder Tr. at 631A-33A. Lethargy as a result of illness and dehydration was a much more reasonable explanation for Colten's behavior at that point. Snyder Tr. at 633A-34A.

7. Post-Hospitalization to PDD-NOS Diagnosis.

Doctor Bradstreet testified that Colten never really recovered from this illness. Snyder Tr. at 160. Mrs. Snyder testified that, after Colten's release from the hospital, he continued to lose weight. She described him as very cranky and fussy. He cried all night long. Snyder Tr. at 52A. The medical records partially support and partially contradict her testimony.

After discharge from the hospital, Colten returned to Dr. Sahai on June 2, 1998. At this post-hospitalization check up, Colten appeared to be doing "quite well," and Mrs. Snyder described him as almost back to normal. His physical examination was normal, although his throat appeared to be mildly erythematous. Based on the recommendation of the specialist who saw Colten in the hospital (*see* Snyder Pet. Ex. 10, p. 18), Colten was prescribed Bactrim for 30 days. Snyder Pet. Ex. 8, p. 94.

On June 10, 1998, Colten was seen again by Dr. Sahai, this time for two days of fever. His temperature was elevated at 102 degrees. His right cervical lymph nodes were slightly enlarged. Doctor Sahai recorded a history of a "very erythematous

appearing viral xanthum that lasted a few days," but did not record when it began. His throat was noted to be mildly erythematous and his tympanic membranes showed poor mobility bilaterally. Colten weighed 24 pounds, 13 ounces. Doctor Sahai noted that, in a little over a month, Colten had lost a pound in weight.[444] His knees and ankles appeared to be warmer, and Dr. Sahai considered juvenile rheumatoid arthritis as a possible diagnosis. He suggested a consultation with a pediatric endocrinologist, indicating that Colten "appears quite ill and does not appear to be improving...". He prescribed a ten day course of Augmentin, another antibiotic. Snyder Pet. Ex. 8, pp. 92-93.

Colten saw Dr. Ayodeji Otegbeye[445] the next day, June 11, 1998. His examination disclosed no joint swelling or redness, but he did find a faint skin rash on Colten's trunk that appeared to be recurrent.[446] Colten was described as somewhat apathetic, with an intermittent dry cough. His neurologic exam showed no focal deficits. At 17 months of age, Colten had only a three word vocabulary consisting only of names.[447] Doctor Otegbeye requested that Mrs. Snyder keep a journal of four daily temperature readings and that she note any mouth sores. His impression was recurrent fevers with pharyngitis, and his differential diagnoses included cyclic

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[444] Colten had actually lost more than three pounds since April 7, 1998, when he was recorded as weighing 27 pounds, 7 ounces. Snyder Pet. Ex. 8, p.118. He lost weight between April 7 and his MMR vaccination on April 23, 1998, when he weighed 25 pounds, 14 ounces. Snyder Pet. Ex. 8, p. 115. He regained some weight after the MMR vaccination, as he was recorded at 26 pounds, 2 ounces on both May 19 (Snyder Pet. Ex. 8, p. 92) and May 24, 1998 (Snyder Pet. Ex. 10, p. 43). His weight dropped by May 25, 1998, to 25 pounds, 9 ounces (Snyder Pet. Ex. 11, p. 38), reflecting the beginning of the gastrointestinal illness that caused his dehydration and prompted his hospitalization. His weight was not recorded during his hospitalization or at the June 2, 1998 followup visit, but by June 10, 1998, he had lost two pounds and four ounces since early April. Snyder Pet. Ex. 8, p. 92. Colten actually gained weight between his MMR vaccination and the emergency room visit two days before his hospitalization.

[445] Presumably, Dr. Otegbeye was the pediatric endocrinologist Dr. Sahai referenced, but none of the records reflect Dr. Otegbeye's specialty.

[446] A recurrent rash would be consistent with Colten's history of developing various rashes, many in apparent response to milk products. *See, e.g.*, Snyder Pet. Exs. 11, p. 49; 7, pp. 58-60; 8, pp. 111, 129.

[447] This contemporaneous report of Colten's vocabulary contrasts with Mrs. Snyder's statements to Dr. Bradstreet that he had a large vocabulary and early speech. *See* Snyder Pet. Ex. 12, pp. 641-42. There was no indication in Dr. Otegbeye's record that Colten had recently lost words or expressive language in general. A three word vocabulary at 17 months of age is not typical. The MacArthur Communicative Development Inventory, a widely used scale to assess language and communication development in infants, indicates that most children have a 20 word vocabulary at 14-15 months of age. Cedillo Res. Tr. Ex. 8, p. 33; Cedillo Tr. at 1329-30A.

neutropenia,[448] Behcet's syndrome,[449] or recurrent viral infections. Snyder Pet. Ex. 8, pp. 89-91.

Extensive laboratory testing revealed several abnormal results. Colten's IgA levels were low. His lymphocyte numbers were high, as were his eosinophils.[450] His sedimentation rate was just slightly elevated.[451] Several other tests (alkaline phosphatase ["ALP"] and serum glutamic-oxaloacetic transaminase ["SGOT" or "AST"]) were also elevated. His rheumatoid factor ["RF"] was mildly elevated.[452] Snyder Pet. Exs. 11, pp. 32-37 and 9, pp. 4-13.

On June 29, 1998, Colten was seen again by Dr. Sahai for pulling at his right ear. He had no observable ear infection, and was diagnosed with ear pain associated with a viral syndrome. Doctor Sahai noted that Colten seemed to be rebounding well from his previous illness, having gained weight, and that his parents agreed he appeared to be developing "quite well." Snyder Pet. Ex. 8, p. 82.

Colten received a DTaP vaccination on July 8, 1998. Snyder Pet. Exs. 8, p. 80; 5, p. 1. At this 18 month check up, Colten's height was in the 85th percentile, his weight in the 10th percentile (23 pounds, 12 ounces), and his head circumference in the 25th percentile. Doctor Sahai noted that he had lost quite a bit of weight, and urged Mr. and Mrs. Snyder to follow up with Dr. Otegbeye because of the mildly elevated rheumatoid factor. Although his parents reported that Colten was eating well, Dr. Sahai indicated that the weight loss was of concern. Snyder Pet. Ex. 8 , p. 80. There was no mention

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[448] A periodically low level of neutrophils in the blood, accompanied by fever and various infections. DORLAND'S at 1260-61.

[449] Behcet's syndrome is a chronic inflammatory disorder. DORLAND'S at 1811.

[450] Eosinophils are a type of inflammatory cell. They are normally present in the blood at low levels and move into tissue as part of an allergic response. Hazlehurst Tr. at 621A.

[451] A sedimentation rate test (sometimes referred to as an "ESR" or "Sed Rate") is a non-specific (non-diagnostic) test to detect acute and chronic infections. It is a measurement of how fast red blood cells in solution settle. Some diseases increase the protein content in blood plasma, causing the red blood cells to stick together, which in turn causes them to settle faster. In inflammatory autoimmune diseases, as the disease worsens, the sedimentation rate also worsens. Increased sedimentation rates are associated with renal failure, some forms of cancer, bacterial infections, and severe anemia, among other illnesses. MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS ["MOSBY'S LABS"] at 233-35 (3d ed. 2006).

[452] A rheumatoid factor ["RF"] test is a nonspecific test. It may be elevated in autoimmune diseases, chronic viral infections, mononucleosis, and some bacterial infections, and is usually elevated in juvenile rheumatoid arthritis. MOSBY'S LABS at 462-64. Although one of Dr. Bradstreet's reports (Snyder Pet. Ex. 1 at 4) characterized an elevated RF as indicative of a measles brain infection, Drs. Zweiman and Ward both took issue with this statement. *See* Snyder Res. Exs. C at 2 (Report of Dr. Zweiman) and K at 7. Doctor Ward testified that, in isolation, an elevated RF has almost no meaning. Snyder Tr. at 966A.

of a loss of words or a decline in communicative ability at this visit.[453] Although Dr. Sahai recommended an immediate follow up with Dr. Otegbeye, there is no record of any follow up appointment with him.

Doctor Sahai's office staff contacted the family to check on Colten on July 15, and July 21, 1998, to confirm that he was well. The family reported that he had been febrile for two days, but was afebrile by July 16, 1998. Snyder Pet. Ex. 8, pp. 78-79.

Colten's next visit occurred when he was 20 months old, on September 21, 1998. He saw a physician's assistant in Dr. Sahai's office for a three day fever and loose stools that began on the day of the visit.[454] His parents reported that he had been complaining of right ear pain over the weekend and that the ear had a malodorous discharge that morning. Colten was described as extremely pale. His right eardrum appeared to have ruptured in response to right otitis media. He was prescribed Augmentin. Snyder Pet. Ex. 8, p. 77.

He returned three days later with reports that he was fussy at night. The right ear appeared to be healing, although the left tympanic membrane was mildly erythematous. He was described as "quite active" and in no apparent distress at this visit. Snyder Pet. Ex. 8, p. 76.

His ears were rechecked again on October 8, 1998, with right otitis media noted. Colten was described as pale, with a bloody crusting discharge from his right ear. He was referred to an ear, nose, and throat specialist. Snyder Pet. Ex. 8, pp. 73-74. Colten was seen again by a physician's assistant at Dr. Sahai's office on October 22, 1998, to recheck his ears. He was described as pale, extremely active, and doing well. His right ear was improving. Snyder Pet. Ex. 8, pp. 70-71.

The same physician's assistant saw Colten again on November 9, 1998. He had a build up of ear wax in both ears. Another note about a possible referral to an ENT specialist was included, and because he was pale, blood tests were suggested. Snyder Pet. Ex. 8, p. 69. Two days later, Colten was taken to the emergency room for right ear pain, a fever of 102.2 degrees, and conjunctivitis in his right eye. He was diagnosed with otitis media and prescribed Amoxicillin. Snyder Pet. Ex. 8, p. 68.

Doctor Sahai saw Colten the next day at his office, where his fever from the previous evening was described as 104 degrees. Doctor Sahai described Colten as "[r]unning around the office, very happy, playful, spitting out a few words." He had a

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[453] On July 28, 1999, Dr. Bradstreet's history recorded that Colten lost his speech at approximately 18 months of age. Snyder Pet. Ex. 11, pp. 32-37.

[454] Other than the gastrointestinal illness that prompted his hospitalization on May 26, 1998, this is the first report of diarrhea or loose stools after his MMR vaccination. Colten's previous gastrointestinal illnesses had primarily involved vomiting, rather than diarrhea.

large plug of ear wax in his right ear that was removed with some difficulty. His throat was mildly erythematous and he was quite pale. Doctor Sahai assessed Colten as having a "viral syndrome" and teething. Snyder Pet. Ex. 8, p. 67.

Mrs. Snyder's testified that Colten's loss of appetite, disturbed sleep pattern, diarrhea, repetitive play, and loss of vocabulary and mobility following the MMR vaccination precipitated the visits to Dr. Sahai's office and the emergency room in the months following his MMR vaccination and hospitalization. Snyder Tr. at 49A-50, 53A-55A. The records summarized above note none of these symptoms, except for one reference to loose stools on the date of the visit. "Running around the office" is not compatible with a loss of mobility. The primary complaint between Colten's discharge from the hospital and his two year check up was recurrent otitis media with accompanying fever.

Doctor Bradstreet testified that Colten seemed to be getting more infections after April, 1998, with approximately one infection per month after the vaccination. Snyder Tr. at 171. In fact, Colten's post-MMR pattern of infections was not markedly different from his pre-MMR pattern: Colten had monthly infections from February through May, 1997, various infections in December, 1997, and infections again in February through April, 1998. After the MMR vaccination, he had some infections in May through July, 1998, and in September through November, 1998. His two year well-child check up took place in January, 1999.

8. PDD-NOS Diagnosis.

On January 27, 1999, Colten had his two year well-child check up. His height was in the 95th percentile, his weight in the 50th percentile, and his head circumference was in the 75th percentile. The office note recorded Mrs. Snyder's concerns regarding tantrums, discipline, and developmental milestones. She described Colten as "not cooperative" and having some trouble with his speech. She indicated that Colten was speaking relatively well, but at around 19 months, he seemed to arrest his progress, and was no longer speaking well. This appears to be the most contemporaneous account of the timing of Colten's loss of language. Snyder Pet. Ex. 8, p. 66. If Mrs. Snyder also mentioned chronic diarrhea or loose stools, Dr. Sahai did not record it.

Doctor Sahai noted an avoidance of eye contact, describing it as "very aberrant compared to what we normally see in Colten." He also noted a right-sided weakness, with leg-dragging when he walked and less strength in his right hand than his left hand. He referred Colten to a pediatric neurologist and Easter Seals for motor and speech delays. Snyder Pet. Ex. 8, p. 66.

Mrs. Snyder testified that she had previously brought her concerns to Colten's pediatrician, telling him that Colten was not responding to his name or listening to her. She thought it might be a hearing issue. Snyder Tr. at 55A. She testified that, after Colten's two year checkup, the pediatrician finally agreed that there was something

going on with Colten, and made a referral for a developmental evaluation. Snyder Tr. at 56A. Doctor Bradstreet testified that Mrs. Snyder told him that she was trying to get the pediatrician to respond to her concerns, but that he "blew her off." The reports Dr. Bradstreet filed (Snyder Pet. Exs. 1, 17, 18, and 26) were even more critical of Dr. Sahai's care of Colten.

However, this testimony contrasts with Mrs. Snyder's comments about Colten's pediatrician on Dr. Bradstreet's intake form. On May 11, 1999, she wrote: "I was very lucky to have a pediatrician who had deep concern for the way Colten was not progressing/regressing. He referred us to early intervention where [Colten] was evaluated." Snyder Pet. Ex. 12, pp. 641, 644.

The testimony of Mrs. Snyder and Dr. Bradstreet on this point also conflicts with the tenor of the medical records themselves, which reflect that Dr. Sahai was a concerned and caring physician. He secured an immediate referral to Dr. Otegbeye, with a next-day appointment. He called the family to determine how the appointment went, and also talked with Dr. Otegbeye himself. Snyder Pet. Ex. 8, p. 88. He urged the family to follow up with Dr. Otegbeye when Colten did not seem to be recovering from the illness that prompted the original referral. *Id*., p. 80. There were several telephone calls to the family to check on Colten during July, 1999. *Id.*, p. 78-79.

Following his two year well-child visit, Colten had several office and emergency room visits for ear infections,[455] cough, low grade fever, vomiting, and diarrhea. Snyder Pet. Exs. 8, pp. 49, 60; 7, p. 57; and 11, pp. 23-27, 14, pp. 37-42. At the Halifax emergency room on March 12, 1999, the treating physician, Dr. Jaime Quiteros, noted: "The child appears to have lack of social skills for age. He is currently being evaluated for developmental delay. It seems like the child spoke repeated words until the age of 12 months, and after that the child entirely stopped talking. According to the father, it is something that is rather unique in him. He does not seek social interaction with other children. The child at this point does attend day care. To communicate, the child points with his fingers or makes gestures." Doctor Quiteros also noted that Colten did not speak a single word in the ER, but communicated with his mother by sounds. Colten was febrile and mildly dehydrated. Doctor Quiteros discussed his concerns about developmental delay with Colten's parents, telling them that it was likely that Colten had autism. Snyder Pet. Ex. 11, pp. 23-27. Laboratory testing showed a bacterial infection. Snyder Pet. Ex. 11, pp. 28-29. A recheck at the Halifax emergency room on March 13, 1999, showed that Colten's fever was resolving. He had occasional diarrhea, but no vomiting. Snyder Pet. Ex. 11, pp. 14-15.

Doctor Sahai saw Colten again on March 18, 1999, for "re-evaluation of vomiting,

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[455] Doctor Bradstreet testified that the recurrent otitis media was a new condition for Colten, one that he had not experienced prior to his MMR vaccination. Snyder Tr. at 171. He was incorrect; Colten was seen for otitis media in February, 1999, two months before his MMR vaccination. Snyder Pet. Ex. 11, pp. 46-48.

diarrhea episode." He noted that Colten had not yet had the Easter Seals evaluations, and commented that Colten "does not appear to have a pervasive development disorder but hearing is my concern at this time." Snyder Pet. Ex. 8, p. 49.

On March 25, 1999, Colten was finally evaluated for the speech and motor delays Dr. Sahai documented two months earlier. His parents wrote on his intake form: "We are concerned about Colten's speech and language development. He only has a 3-5 word vocabulary. He does not use 2 words together in a phrase. He will obey some commands. He used to use more words when he was younger but then stopped...". In addition to the speech and language problem, they listed temper tantrums and interpersonal relations as their concerns about Colten's development. Snyder Pet. Ex. 8, p. 43. They made no mention of chronic diarrhea or loose stools.

Testing by the early intervention team disclosed that Colten's language skills were at the level of a nine month-old, a significant delay for a child then 26 months old. His motor development was at an age equivalent of 22 months. In the domains of communication, daily living skills, socialization, and motor skills, Colten showed significant delays. He was recommended for psychological evaluation, an exceptional educational program, audiological evaluation, speech therapy, and parental education. Snyder Pet. Ex. 8, pp. 39-48. Doctor Wiznitzer explained the significance of this testing as measuring Colten's achievements at that specific point in time, noting that the tests did not measure what Colten was capable of achieving. Snyder Tr. at 642A.

Colten began receiving therapy at First Step Therapeutics on April 6, 1999. Snyder Pet. Ex. 8, p. 38. He received a psychological evaluation on August 20, 1999. Doctor Nancy Wenk, who performed part of Colten's initial evaluation in March, 1999, noted that Colten was wandering around restlessly during the screening, showed limited social interaction, and exhibited a failure to follow directions. Mrs. Snyder reported a loss of communication skills at 15 months of age. She described Colten as lining up toys and having intense emotional reactions to change. Mrs. Snyder reported that "following an MMR shot, he was hospitalized for tonsillitis-pharyngitis with a high fever for seven days" and that after antibiotic administration, Colten screamed for 22 out of 24 hours. In a slight conflict with her earlier report that Colten lost communication skills at 15 months, Mrs. Snyder also reported that he stopped talking at the time of his hospitalization (Snyder Pet. Ex. 13, p. 6), which actually occurred when he was 16-17 months of age. Although he scored 36 on the Childhood Autism Rating Scale ["CARS"], which placed him in the mild to moderately autistic range, Dr. Wenk's diagnostic impression was that Colten had a pervasive developmental disorder, but not at the intensity or frequency of symptoms necessary to meet the diagnostic criteria for autistic disorder. She recommended a number of treatment and therapy options. Snyder Pet. Ex. 13, pp. 5-8.

Doctor Bradstreet noted that Colten had not made much progress between the March 1999 evaluation and the August 1999 evaluation. His scores on the Vineland Adaptive Behavior Scales were similar, and only slightly improved by August, 1999,

although he was five months older and had begun speech therapy four months earlier. Snyder Pet. Ex. 13, pp. 23 and 7; Snyder Tr. at 182.

C. Colten's Treatment After PDD-NOS Diagnosis.

1. Speech Therapy.

Ms. Timlin first saw Colten for speech therapy on April 13, 1999. She remained his therapist until he was discharged from therapy in May, 2002.[456] *See* Snyder Pet. Ex. 14, p. 2. She initially assessed Colten as having a severe language delay. Snyder Tr. at 103, 109-10, 127, 136.

She began teaching Colten how to communicate, and teaching his parents how to reinforce the lessons at home. Snyder Tr. at 111. Colten's behavior made this difficult. In early sessions, he would not sit at the table and had to be cajoled into participating. His play was repetitive and ritualistic. He responded to interruptions in his playing with temper tantrums. She could not approach Colten any closer than three to four feet without him moving away. Snyder Tr. at 112-14. He would permit eye contact if there were something he wanted, but would otherwise look sideways and up and down the wall rather than at her. Snyder Tr. at 114.

Ms. Timlin saw Colten for 30 minutes of therapy twice a week. Initially, Colten progressed slowly. She believed that the pace of Colten's progress improved once he was placed on the gluten- and casein-free ["GFCF"] diet. Snyder Tr. at 115-17. According to her notes from May 28, 1999, Colten was on the GFCF diet on that date. Snyder Pet. Ex. 14, p. 67. Thereafter, Colten appeared to be more compliant and less irritable.[457] Snyder Tr. at 116. Ms. Timlin testified that upon review of her notes, she could see significant progress from one month to the next. Snyder Tr. at 117.

Colten's improvement began in June, 1999. He began speaking true words at that time. Snyder Tr. at 117, 119-20. On June 1, 1999, he didn't scream. The rings under his eyes were disappearing and he was playing better. On June 11, 1999, Colten did not display any ritualistic behaviors. Snyder Tr. at 117. Notes from July 6, 1999, reflected improved behavior, more smiles, and increased eye contact and parallel play. Snyder Tr. at 120. She noted that she could "beg[in] to see effects of GFCF diet" on July 27, 1999. Snyder Pet. Ex. 14, p. 65. These improvements all occurred before Colten first saw Dr. Bradstreet.

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[456] Colten received school-based language therapy until October 2003. Snyder Pet. Ex. 15, pp. 172-73. He was dismissed from school-based speech therapy in May, 2007. *Id*., pp. 72-74.

[457] Other records reflect that milk and casein products were removed from his diet at the end of March, 1999, and gluten products were removed on May 9, 1999. Snyder Pet. Ex. 12, p. 642. However, Ms. Timlin's notes reflected that she first talked to Mrs. Snyder about the diet on May 4, 1999. Snyder Pet. Ex. 14, p. 67.

At some point, Ms. Timlin became aware that Colten was seeing Dr. Bradstreet, although she could not recall exactly when. Snyder Tr. at 118-19. She also became aware that Colten was receiving IVIG therapy, but she did not recall when that therapy began. Snyder Tr. at 121.

When Colten was about 34 months old, Ms. Timlin began to see more imitations of single words. In October, 1999, she was unable to conduct a scored evaluation of him, but recorded the improvements she saw. Her notes reflected that occasionally, and usually when he had a secretin infusion, Colten could appropriately use a three word sentence. Snyder Tr. at 121-23.

By the end of November, 1999, she noted more echoic behavior, but Colten was also putting two syllables together to form a word. By the end of December of that year, Colten was spontaneously using words and phrases and responding to questions. Snyder Tr. at 123-24. Ms. Timlin indicated that Colten's progress by April, 2000, was significant and that it was rare for her to see that degree of progress. Her only other experience with similar progress was with another child on the GFCF diet. Snyder Tr. at 124-25. She noted that, anecdotally, children with behavioral issues and language disorders often improve their behavior if their language improves. Snyder Tr. at 132. Most of her patients improved their speech to the extent of their intellectual and cognitive abilities. Snyder Tr. at 129.

In March, 2000, Colten made spontaneous requests, with improved intelligibility in his speech. Snyder Tr. at 125-26. She recorded that he had received an IVIG treatment on the Wednesday prior to this particular session. In her opinion, the treatment had a positive effect on his performance at that session. Snyder Tr. at 126.

Ms. Timlin was aware that there were times when Colten was not receiving IVIG treatment for financial reasons, but she did not document those periods. There were times when he became significantly frustrated during his speech therapy, and she attributed that to not receiving IVIG, but this was not reflected in her notes. Snyder Tr. at 126-27. She admitted that she could not track the ups and downs in Colten's progress with the dates of secretin or IVIG infusions, except when her notes reflected a treatment or a gap in the treatment. On August 11 and 22, 2000, she noted that Colten was not himself, but she did not record any treatment.[458] On December 5, 2000, she noted that his intelligibility was significantly clearer,[459] with similar notations on March

[458] He began chelation sometime between August 3 (*see* Snyder Pet. Ex. 12, p. 543, when prescription is dated), and August 7, 2000 (*see id.*, p. 528, noting on August 14, 2000, that he had finished chelation a week earlier), but had difficulties with the chelation, as noted in Dr. Bradstreet's records. *Id.*, p. 528, and discussion of the chelation treatment in Part C.3.b.(2)(c), below.

[459] He received secretin, and was prescribed a chelating agent on December 4, 2000. Snyder Pet. Ex. 12, pp. 508-09.

20, 2001.[460] On June 5, 2001, his behavior was a problem, and, on June 12, 2001, she noted that he had an IVIG treatment the day prior, the circles under his eyes were decreased, and his behavior was improved. July 17, 2001, was a particular high point because Colten was playing with imagination.[461] On August 22, 2001 and on October 10, 2001, her notes reflected more complex play strategies.[462] Snyder Tr. at 134-35.

Ms. Timlin testified that Colten had some significant peaks and valleys in his progress, but her notes reflected only one period of clear decline. She agreed that her notes reflected a significant, steady improvement in Colten. Snyder Tr. at 137.

Given that Colten was seeing Ms. Timlin twice a week for therapy and making fairly steady progress, and that Colten was receiving IVIG treatments at approximately six to eight week intervals and secretin infusions monthly, it would not be unusual for the treatments and speech improvements to coincide without any causal relationship between the two events.

Colten's language skills began improving after he started speech therapy. Ms. Timlin's notes reflected improvement by July, 1999. As Dr. Wiznitzer testified, children with language problems, whether or not related to an ASD, improve with intervention. How well they respond to speech therapy is related to their level of intellectual and cognitive abilities. Snyder Tr. at 640A-41A. Colten's cognitive potential was in the normal range, which gave him the capacity to improve as much as he did. Snyder Tr. at 641A-42A. A child with an IQ of only 50 would not have made the same improvements. Snyder Tr. at 642A.

2. GFCF Diet.

The GFCF diet involves the elimination of wheat and milk-based products from the diet. Colten began the diet shortly after he began seeing Ms. Timlin for speech therapy. According to Ms. Timlin, she referred Mrs. Snyder to the mother of another of her patients, who recommended the GFCF free diet. Snyder Tr. at 62-63. After speaking with the other mother, Mrs. Snyder immediately placed Colten on the diet. Snyder Tr. at 63. According to Mrs. Snyder, she removed gluten and casein products from his diet after a recommendation by his speech therapist, with a "very good

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[460] Colten had last received an IVIG treatment on March 2, 2001. Snyder Pet. Ex. 12, pp. 492-96.

[461] Colten had received a secretin infusion on July 6, 2001, but was five to six weeks post his last IVIG treatment. Snyder Pet. Ex. 12, pp. 479, 485-87. Mrs. Snyder noted that Colten's performance and behavior generally deteriorated six weeks after IVIG treatment. *Id*., p. 266.

[462] Colten had received an IVIG treatment on August 6, 2001 (Snyder Pet. Ex. 12, pp. 473-76) and a secretin infusion on September 21, 2001 (*id*., p. 464), but he was over two months past his most recent IVIG infusion at the October 10, 2001 therapy session.

response."[463] Snyder Pet. Ex. 12, pp. 604-05.

Mrs. Noonan testified that she saw minor positive changes in Colten's behavior after he was placed on the diet. She commented that Colten could become irrational if he ate so much as a small goldfish cracker. Snyder Tr. at 94. Colten continued on the diet, and was still on the diet at the time of the hearing. Snyder Tr. at 76.

In Dr. Wiznitzer's experience, improvements on the CFGF diet are found only in those children who have milk or gluten intolerance. Snyder Tr. at 674A. Colten's milk intolerance, which predated his MMR vaccination, was well-documented in his medical records. Snyder Tr. at 675A. Testing suggested that Colten reacted adversely to gliadorphin (wheat), in addition to milk. Snyder Pet. Ex. 12, p. 613. According to Dr. Wiznitzer, the diet did not treat his autism; it treated a food intolerance or allergy that was aggravating his behavior and making him miserable. Snyder Tr. at 675A.

3. Treatment by Dr. Bradstreet.

Doctor Bradstreet began treating Colten on July 28, 1999, and was still treating him at the time of the hearing in November, 2007. Colten's medical records with Dr. Bradstreet encompass over 650 pages over more than eight years, including over 160 office visits, telephone consultations, and email contacts, regarding Colten's condition, symptoms, treatments and response to those treatments.[464] These records reflected office visits every four to eight weeks throughout most of the period between mid-1999 and August, 2007, the date of the last medical record filed.

Doctor Bradstreet's treatments included a wide variety of dietary supplements,[465] secretin infusions, immunoglobulin therapy, chelation, glutathione, and prednilisone. He ordered numerous laboratory tests, many of which were non-standard tests not approved by the FDA, or ones performed outside the U.S.[466] He performed several lumbar punctures to draw Colten's CSF to test for measles virus and measles

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[463] The history form completed for Dr. Bradstreet indicated that milk and casein products were eliminated the end of March, 1999, and gluten products were eliminated on May 9, 1999. Snyder Pet. Ex. 12, p. 642. The end of March date conflicts with Ms. Timlin's records which reflect that she told Mrs. Snyder about the diet on May 4, 1999. Snyder Pet. Ex. 14, p. 67.

[464] These records do not include Dr. Bradstreet's hyperbaric oxygen treatments. Although the hyperbaric oxygen treatments are referenced occasionally in the other medical records (*see, e.g.*, Snyder Pet. Exs. 7, pp. 22-24 and 12, pp. 1, 103), they were not furnished with the rest of the records from Dr. Bradstreet. Snyder Tr. at 278A-79.

[465] Snyder Res. Tr. Ex. 1 contains a list of medications and dietary supplements prescribed for Colten between 1999-2004. *See also* Snyder Tr. at 228A-37A (Dr. Bradstreet's testimony discussing some of the supplements).

[466] *See, e.g.*, Snyder Pet. Ex. 12, pp. 249 and 529, and Snyder Pet. Ex. 207, pp. 3-6.

antibodies, and referred Colten to a gastroenterologist for a colonoscopy and gut biopsy. His reported diagnoses varied throughout Colten's treatment. He began with a diagnosis of autism, yeast overgrowth, and a fungal infection in July, 1999.[467] Snyder Pet. Ex. 12, pp. 607-09. Subsequent diagnoses included autoimmune encephalopathy (Snyder Pet. Ex. 12, p. 583, in March, 2000); autoimmune disease not elsewhere classified and immune mechanism disease not elsewhere classified (*id*., p. 353, in December, 2002); allergic gastroenteritis and autoimmune disease (*id*., p. 313, in March, 2003); unspecified urticaria,[468] unspecified encephalopathy, and allergic gastroenteritis (*id*., pp. 299-300, in April, 2003); encephalopathy unspecified, unspecified disorder of immune mechanism, gastroenteritis, and colitis[469] (*id*., p. 272, in July, 2003); disturbance of sulphur-bearing amino acid metabolism, unspecified disorder of immune mechanism, unspecified disorder of metabolism, and encephalopathy unspecified (*id*., p. 206, in June, 2004); the same diagnoses in July, 2004, with the addition of "rule out epilepsy, unspecified" (*id*., p. 191-92); autoimmune disease not elsewhere classified, unspecified disorder of metabolism, unspecified disorder of immune mechanism, and encephalopathy not elsewhere classified (*id*., p. 164 in January, 2005); and toxic effect of mercury and its compounds, autoimmune disease not elsewhere classified, and unspecified disorder of immune mechanism (*id.*, p. 52 in September, 2006). Doctor Bradstreet testified that the recorded diagnoses varied, depending on the nature of the problem being treated at that particular time.[470] Snyder Tr. at 266-68.

Doctor Bradstreet's treatment of Colten overlapped with Colten's speech therapy from July, 1999 through April, 2003. Colten also saw his primary care provider and occasionally saw specialists during this time frame.

Exactly how Mrs. Snyder was referred to Dr. Bradstreet is unclear. Ms. Timlin

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[467] I note that Dr. Wenk concluded that Colten did not meet the diagnostic criteria for autism, giving him a PDD-NOS diagnosis shortly after Colten's first visit to Dr. Bradstreet. Snyder Pet. Ex. 13, p. 7; Snyder Tr. at 184. Doctor Bradstreet's records do not reflect the use of any of the autism rating scales, such as the ADI-R, CARS, or ADOS; his diagnosis appeared to be based solely on his own observations and parental reports.

[468] Urticaria refers to a vascular reaction in the upper dermis, characterized by wheals. DORLAND'S at 1994. Colten was previously treated for hives by another provider (Snyder Pet. Ex. 12, pp. 431-34), and experienced a recurrence in this time frame. Snyder Pet. Ex. 12, p. 302.

[469] Doctor Bradstreet first testified that Dr. Thek, Colten's gastroenterologist, diagnosed him with colitis. He immediately qualified his testimony to reflect that the diagnosis might have been based on the symptoms he presented with that day. Snyder Tr. at 269A. Doctor Thek, Colten's gastroenterologist, never diagnosed colitis. *See* Snyder Pet. Ex. 36, pp. 1-2. His letter to Dr. Bradstreet, specifically stating that there was no evidence of colitis on pathology, was included in Dr. Bradstreet's records. Snyder Pet. Ex. 12, p. 292.

[470] This list is not exhaustive of the various diagnoses assigned to Colten throughout Dr. Bradstreet's treatment of him.

testified that she referred Mrs. Snyder to another mother whose child was seeing Dr. Bradstreet. She admitted that she "made suggestions that he was available," but did not recall any direct referrals to Dr. Bradstreet. Snyder Tr. at 130-31A. Mrs. Snyder testified that Colten's speech therapist told her that she "needed to see Dr. Bradstreet" and that she obtained his contact information from the therapist. Snyder Tr. at 60-61. The questionnaire she completed for Dr. Bradstreet mentioned an Orlando conference where Dr. Bradstreet suggested certain testing, and it also stated that Ms. Timlin "educated her on the different causes of autism" and prompted her to see Dr. Bradstreet while Colten was still young. Snyder Pet. Ex. 12, p. 644. Ms. Timlin's notes did not mention a referral to Dr. Bradstreet.

In the summary of Colten's post-diagnosis and treatment provided below, I have focused primarily on those matters either directly or circumstantially relevant to the issue of causation. The records are voluminous, and while I have read each medical record, school record, and test report submitted, I have not attempted to summarize them all.

a. Colten's Initial Testing and Assessment.

Although Colten did not see Dr. Bradstreet until July 28, 1999, his mother completed a screening evaluation form for treatment on May 11, 1999. A number of laboratory tests were performed at the initial screening visit. In her parent questionnaire, Mrs. Snyder described Colten as having early speech and a large vocabulary, which he lost at approximately 18 months of age. She described his vocabulary exclusively in terms of names (grandma, Krista, mama, dada). She indicated that he stopped playing with his siblings and had delayed motor skills after 16 months of age.[471] She listed chronic "loose stools" as a concern, but noted communication and behavior problems as her primary concerns. She had removed gluten and casein products from his diet after a recommendation by his speech therapist, with a "very good response." Mrs. Snyder described her belief that Colten's problems were linked to his milk allergy, a lot of antibiotic use, and his MMR shot.[472] She recorded that Colten was hospitalized two weeks after the MMR vaccination.[473] Snyder Pet. Ex. 12, pp. 604-09, 633-35, 641-44.

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[471] This report of delayed motor skills may reflect the left-side weakness Dr. Sahai observed at Colten's two year well-child visit. However, it contrasts with Mrs. Snyder's responses to a questionnaire she completed for enrollment in Florida's family support plan. On March 25, 1999, Mrs. Snyder listed under "Colten's Strengths" his motor skills, including his ability to climb, run, and jump well. Snyder Pet. Ex. 13, p. 15.

[472] Mrs. Snyder responded to a question on the form: "Do you believe your child's symptoms are vaccine related?" by circling "yes." She then wrote in the comments about the MMR vaccine, milk allergy, and antibiotic use. Snyder Pet. Ex. 12, p. 642. Doctor Bradstreet testified that this question had been on his intake form for 10 years, and about 40-60% of his patients answered it "yes." Snyder Tr. at 219A.

[473] The hospitalization actually occurred 33 days after the MMR vaccination.

Colten had a number of tests during May, 1999, including antifungal sensitivity, stool analysis, and bacterial sensitivity testing. Snyder Pet. Ex. 8, pp. 21-27. An immune system panel test was also performed which showed normal IgG levels, low IgA subclass levels,[474] and a very high IgE level. Snyder Pet. Ex. 12, pp. 618-22. Allergy testing demonstrated extreme reactivity to trees, grass, weeds, and mold. As Dr. Sahai later characterized Colten's allergy test results: "Colten is allergic to the Florida environment." Snyder Pet. Ex. 8, p. 11.

During his initial examination of Colten, Dr. Bradstreet found him to be combative and agitated. He was unable to obtain vital signs or to check his height and weight. While Colten made good eye contact, it was fleeting. He had social interest in his mother, but not in anyone else. He was hyperactive, toe walking, and engaged in self-stimulatory behavior. His speech was limited to two or three words.[475] In physical appearance, he was thin with dark circles under his eyes. Doctor Bradstreet's working diagnosis was autism, overgrowth of yeast in his digestive tract, and clostridia bacteria in his urinary tract.[476] Snyder Tr. at 147-48, 181, 223A. His later testimony confirmed that his diagnosis was autism, in terms of the DSM-IV-TR, 299.00, diagnostic criteria, rather than the PDD-NOS diagnosis he was later given by Dr. Wenk. Snyder Tr. at 225A-26A.

He began treating Colten initially with intravenous secretin[477] and Diflucan,[478] and a variety of dietary supplements. He referred to Colten's yeast overgrowth as "dysbiosis," meaning that atypical, and possibly pathogenic, organisms were residing in his gastrointestinal tract. Snyder Tr. at 185; Snyder Pet. Ex. 12, p. 609.

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[474] The laboratory report actually listed the IgA results in the "within" range column. Doctor Zweiman testified that this was a "modestly decreased" serum IgA level, not an IgA deficiency. Snyder Tr. at 588A-89A. Subsequent studies in other laboratories, including the Shands Medical Center laboratory at the University of Florida, showed normal IgA levels. Snyder Tr. at 589A; Snyder Pet. Ex. 33, p. 4. An IgA deficiency is associated with chronic and persistent sinusitis, ear infections, and pharyngitis, but not with an increased number of colds. Snyder Tr. at 587A-88A.

[475] Clearly, Colten's language development had plateaued, if not actually declined. In June, 1998, about one year earlier, Dr. Otegbeye had described Colten as having only a two to three word vocabulary.

[476] It does not appear that this laboratory actually grew bacteria from Colten's urine. Doctor Bradstreet testified he determined that Colten had bacteria in his urine, "based on organic acid testing for metabolites from clostridium bacteria in his urine." Snyder Tr. at 148. The report identified the marker as increased dihydroxyphenylpropionic analog. Snyder Pet. Ex. 12, p. 640.

[477] Doctor Bradstreet testified that secretin is a neuropeptide, consisting of a sequence of 27 amino acids, that "has effects in the GI tract and the brain," and increases the "outflow of pancreatic digestive enzymes." Snyder Tr. at 230-31A. Colten received numerous secretin treatments over the next eight years, with both Dr. Bradstreet and his parents ascribing positive results for the therapy.

[478] Diflucan is an antifungal agent. Snyder Tr. at 230.

Doctor Bradstreet described Colten as having one to three loose watery stools a day in July, 1999. Snyder Tr. at 185. This met Dr. Bradstreet's criteria for a diagnosis of chronic diarrhea, which would include loose stools over a period of time, usually for more than two weeks. Snyder Tr. at 269A. The secretin treatment seemed to improve his symptoms, as noted by his mother, Dr. Bradstreet, family members, and his speech therapist. Snyder Tr. at 186-87. According to Dr. Bradstreet, in April, 2000, when Colten first began receiving IVIG treatments, he began to make "remarkable dramatic improvements." Snyder Tr. at 188A. Doctor Bradstreet prescribed the IVIG treatments based on the work of Drs. Gupta[479] and El-Dahr. According to Dr. Bradstreet, Colten met the selection criteria for IVIG treatments based on his long history of "immunological dysregulation" and his high level of antibodies to MBP. Doctor Bradstreet testified that, based on Colten's ongoing gastrointestinal problems, his immunologic history, and his regression after 15-16 months of age, Colten appeared to fit the regressive subset of children with autism. Doctor Bradstreet variously described Colten's condition as "autoimmune related encephalopathy" and "post-measles encephalopathy." Snyder Tr. at 189A-90; Snyder Pet. Ex. 12, p. 22.

b. Types of Treatment Provided.

Doctor Bradstreet testified that Colten made a dramatic, and highly unusual, level of improvement while under his care. By six years of age, Colten had normal language scores, which represented a remarkable recovery from the levels he displayed at two and one-half years of age. Snyder Tr. at 192-93A. The progress continued. Although Colten started the first grade classified as developmentally delayed and language impaired (Snyder Pet. Ex. 15, p. 145), at seven and one-half years of age, Colten's vocabulary and sentence structure was that of a nine year old. Snyder Tr. at 194A. Colten was released from the developmental delay classification on August 10, 2004. Snyder Pet. Ex. 15, pp. 116, 125-26.

Doctor Bradstreet based his treatment modalities on his view of what caused Colten's condition. He noted that Colten was exposed to mercury in TCVs, both prior to, and at the time of, his MMR vaccination.[480] Based on the immunological records, the hospitalization, the subsequent treatment, and on other laboratory testing, he

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[479] Doctor Bradstreet may have been referring to Snyder Pet. Ex. 181, S. Gupta, *Immunological Treatments for Autism*, J. AUTISM DEV. DISORDERS 30(5): 475-79 (2000), in which Dr. Gupta discussed positive results from an unblinded trial of IVIG therapy. The article also referenced an ongoing double-blinded trial, using autism rating scales to measure efficacy. If the results from that trial, ongoing in 2000, were ever published, the paper was not filed as evidence in the Theory 1 cases.

[480] The parties stipulated that the level of thimerosal in the Hib vaccination Colten received at the same time as his MMR vaccination could not be determined. Jt. Stip., ¶ 10. Although Colten apparently had few dietary sources for mercury ingestion, his mother testified that he occasionally ate tuna fish prior to his placement on a more restricted diet (Snyder Tr. at 76-77A).

believed the MMR vaccination dysregulated Colten's immune system.[481] Snyder Tr. at 195A. The dysregulated immune system permitted gut and brain inflammation. Snyder Tr. at 195A. The evidence for gut inflammation came from biopsies taken during an endoscopy and a colonoscopy in May, 2002. The evidence for brain inflammation was "his overall cognitive abilities and his response to therapies that are anti-inflammatory in nature." Snyder Tr. at 195A-196. He believed that Colten had oxidative stress, and was certain that he had persistent measles virus in his CSF and gastrointestinal tract. His immune dysregulation, exposure to antibiotics, and persistent virus led to an inability to manage pathogens in his gut. His therapies for Colten were designed to address all of these issues. Snyder Tr. at 196. A more detailed account of the testing performed or ordered by Dr. Bradstreet, the results, and interpretations of those results is immediately below, followed by an account of Dr. Bradstreet's treatment regimen.

(1) Testing.

(a) Low IgA Levels.

One and one-half months after his MMR vaccination, Colten had a low serum IgA (24.9, with a reference range of 36-163 mg/dL as normal). Snyder Pet. Ex. 9, p. 5. According to Dr. Bradstreet, the level was still low in July, 1999, when he retested Colten. Snyder Tr. at 197. The actual test results showed that Colten's total IgA was within normal limits (38 mg/dL, with a reference range of 24-121 as normal). However, IgA subclasses (IgA1 and IgA2) levels were low (31 mg/dL of IgA1, with a reference range of 48-378 and 6 mg/dL of IgA2, with a reference range of 13-91).[482] Snyder Pet. Ex. 12, p. 620. Doctor Zweiman testified that this was a "modestly decreased" serum IgA level, not an IgA deficiency. Snyder Tr. at 588A-89A.

Doctor Zweiman did not think these levels were of concern. Snyder Tr. at 587A-89A. Another physician, Dr. Von Elten, who replaced Dr. Sahai as Colten's primary care provider, did not think that these IgA levels were of any clinical significance. He spoke with Dr. Bradstreet about Mr. and Mrs. Snyder's request that he order the IVIG product. With regard to this conversation, Dr. Von Elten's notes stated "mild IgA subtype deficiency not clinically significant." The note does not reflect who made the

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[481] The only witness who testified that Colten's immune system was dysregulated prior to his MMR vaccination was Dr. Kennedy. When asked if Colten had evidence for immune dysfunction and immune suppression prior to receiving his MMR vaccination, Dr. Kennedy's response was highly equivocal. He testified: "I would say that there was some indication that it might have been possible." He relied on "[s]ome reoccurring infections that appeared to occur, and some of the, the selective IgA that was just one point, but it's, it's not hard evidence but it's suggestive." Snyder Tr. at 366A-67A. When informed that Dr. Bradstreet had testified that Colten's immune system was not dysregulated prior to the receipt of the MMR vaccine, Dr. Kennedy deferred to his assessment. Snyder Tr. at 376.

[482] During the hearing, Dr. Bradstreet referred to Colten's high IgA levels, noting that the inflammation found on biopsy of gut tissue explained those "high" levels. Snyder Tr. at 210-11. This was apparently a misstatement, as he later referred to Colten's low IgA levels. Snyder Tr. at 216.

conclusion regarding the lack of clinical significance. Snyder Pet. Ex. 7, p. 54. Although the context suggests it was Dr. Bradstreet (a conclusion also reached by Dr. Ward upon reading these notes (*see* Snyder Res. Ex. K at 8)), Dr. Bradstreet testified that he did not so conclude. Snyder Tr. at 283A. As these laboratory tests do not appear in Dr. Von Elten's records (Snyder Pet. Ex. 7), the information concerning the IgA levels must have come from Dr. Bradstreet.

An IgA test performed in January, 2006, ordered by Dr. Skoda-Smith, an immunologist to whom Colten was referred, was normal. Snyder Pet. Ex. 33, p. 4. Colten's IgA levels were also normal in July, 2007, in the only other serum IgA test ordered by Dr. Bradstreet. Snyder Pet. Ex. 12, p. 18.

(b) High IgE Levels.

Doctor Otegbeye did not test Colten's IgE levels. Initial testing initiated by Dr. Bradstreet showed an extremely high IgE level (2471 IU/mL with a reference range of 0-164), indicative of an allergic process. Snyder Tr. at 197; Snyder Pet. Ex. 12, p. 619. Doctor Zweiman characterized this result as a strikingly elevated serum IgE level, which Colten's doctors should have followed up with testing to ensure that there was no parasitic infection, which might have caused his diarrhea. Snyder Tr. at 618A-19A. There was no evidence that Dr. Bradstreet conducted such follow up. Although he did stool testing at the initial visit, the analysis did not include testing for parasites. Snyder Pet. Ex. 12, p. 611.

Doctor Zweiman testified that another explanation for Colten's elevated IgE level was eosinophilic gastroenteritis, which is seen in children who have food allergies or other reactions to certain foods, something Colten clearly demonstrated, both clinically and on the gut biopsies taken in May, 2002. Snyder Tr. at 620A; Snyder Pet. Ex. 36, p. 4. The only other IgE testing, conducted on July 16, 2007, showed a level of 820 with the upper range of normal at 328. Snyder Pet. Ex. 12, p. 18.

(c) Lymphocyte Levels.

Doctor Bradstreet characterized Colten's lymphocyte levels as evidencing a persistent lymphocytosis, or too many white lymphocytes, which indicated immune dysregulation. Snyder Tr. at 197. Doctor Otegbeye's testing in June, 1998, showed 67% lymphocytes, with a normal range of 18-56. Snyder Pet. Ex. 9, p. 5. The June, 1999, results showed 62% lymphocytes, with a reference range of 50-56%. Snyder Pet. Ex. 12, p. 622. Colten's lymphocyte levels were consistently high. *See id.*, pp. 68-70, 119-20, 245, 261, 403, and 470. They were low only on one test. *Id.*, p. 36.

(d) Myelin Basic Protein Autoantibodies.

Doctor Bradstreet ordered MBP autoantibody testing at Colten's initial visit in July, 1999 (Snyder Pet. Ex. 12, p. 609), and had Mrs. Snyder sign a consent form for

such testing (*id*., p 632), but the sample was not drawn until January, 2000. Specialty Laboratories reported his result on January 25, 2000, as 46 EIA units, with a reference range for normal of less than 10. *Id.*, pp. 593-94. Mrs. Snyder could not recall why the MBP test was performed. Snyder Tr. at 79.

Doctor Bradstreet characterized Colten's initial MBP autoantibody level as "very high." Snyder Tr. at 197. Doctor Zweiman concurred with this assessment. Snyder Tr. at 585. Doctor Bradstreet recommended a course of IVIG treatment to clear the antibodies and to treat Colten's elevated IgE level. Snyder Pet. Ex. 12, pp. 583-86. According to Dr. Zweiman, IVIG would not be an appropriate therapy to treat an anti-MBP antibody level of 46. Snyder Tr. at 615A.

Doctor Zweiman also noted that measuring antibodies against MBP can be difficult. Snyder Tr. at 574A-75A, 578-79A. It is also difficult to compare findings from one measurement technique to another. Testing for MBP has not been standardized, as the primary use for anti-MBP tests is in research, rather than clinical care. Snyder Tr. at 580.

Anti-MBP antibodies have been reported in patients with ASD and in patients with neurodegenerative diseases or epilepsy,[483] with varying frequency. Some reports indicate that 50-60% of ASD patients have such antibodies. Anti-MBP antibodies have been found in 62% of individuals with multiple sclerosis and in about 50% of those with active rheumatoid arthritis. However, anti-MBP antibodies have also been found in about 25% of individuals without any clinical disease, and thus elevated anti-MBP levels are not always a sign of neurologic dysfunction.[484] Snyder Tr. at 580-82A. There is no evidence that anti-MBP antibodies are associated with any pathology in ASD patients. Since injecting anti-MBP into experimental animals does not induce neurologic disease, there is no consensus on the clinical relevance, if any, of anti-MBP antibodies. Snyder Tr. at 582A-53A.

An MRI can show demyelination in conditions like multiple sclerosis, but demyelination is not seen in autism. Snyder Tr. at 577A-78. Colten's MRI, performed in January, 2006, showed no evidence of demyelination. Snyder Pet. Ex. 33, pp. 9-10. Because normal individuals may have antibodies against MBP, and such antibody levels are highly variable, it is difficult to draw conclusions from Colten's test results. Snyder Tr. at 578-79A.

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[483] Doctor Zweiman noted that the particular study finding anti-MBP antibodies in those with epilepsy that he relied upon was careful to exclude those with ASD from their sample of epileptics. Snyder Tr. at 603A.

[484] An immunologist who evaluated Colten in 2005 also noted that anti-MBP antibodies are suggestive of central nervous system inflammation and damage, but not specific of such disorders. She was informed by Colten's parents of his high MBP levels; she was unaware that Colten's subsequent MBP tests were generally normal. Snyder Pet. Ex. 33, p. 19.

On the date Colten began IVIG therapy, March 8, 2000, Dr. Bradstreet ordered another test of his anti-MBP level.[485] The report was negative. It included the comment: "There was no sign of autoimmunity to brain myelin...." Snyder Tr. at 243A-44; Snyder Pet. Ex. 207, p. 1.

Over the next six years, Colten's blood anti-MBP antibodies remained within the normal range of 10 or below, except for one test on October 9, 2002, when the level was 14. Snyder Pet. Ex. 12, p. 469 (4, on August 6, 2001); p. 357 (14, on October 9, 2002); p. 345 (4, on December 19, 2002); p. 189 (4, on July 28, 2004); and p. 81 (5, on April 24, 2006). Doctor Zweiman noted that anti-MBP levels are variable. Snyder Tr. at 616A. The only test for MBP in Colten's CSF, drawn on April 17, 2002, was also negative. Snyder Pet. Ex. 207, p. 2. Antibodies against MBP in the CSF would be more direct evidence of damage to the white matter of the brain than finding such antibodies in blood serum. Snyder Tr. at 585-86A.

In spite of repeatedly normal anti-MBP tests, apparently Colten's parents still thought his anti-MBP antibodies were high in March, 2007. At his 10 year check up, they reported that he had anti-MBP antibodies to his primary care physician, and attempted to get his IVIG treatment for them restarted. Snyder Pet. Ex. 7, p. 6. Apparently Dr. Bradstreet thought they were still high as well, because a note, dated in March, 2007, in the records of Colten's family practice physician commented: "IVIG referral treatment by Dr. Bradstreet for myelin protein antibody." *Id.*, p. 3. A later-dated note recorded that a request for the IVIG had been sent to another office for processing. *Id.*

Doctor Bradstreet ascribed the need for IVIG therapy to Colten's anti-MBP levels. However, there is no evidence that either the wild-type measles virus or the vaccine strain measles virus induces the formation of anti-MBP antibodies, despite extensive study. It is not a reliable marker for measles infection in the brain. Snyder Tr. at 583A-86A.

(e) Mercury Testing.

Snyder Res. Tr. Ex. 3, p. 7 is a table that captures the mercury testing performed on Colten over more than six years, measuring mercury in the hair, blood, and urine. For reasons set forth below, I conclude that none of these tests demonstrated excess mercury in Colten's body.

[485] These results were dated September 21, 2001, and involved a different testing technique. There was no explanation of why the testing process took over 18 months. Snyder Pet. Ex. 207, p. 1; Snyder Tr. at 585, 613A.

(i) Hair Mercury Test.

Colten's first mercury test was a hair test, conducted on April 29, 2000. Snyder Pet. Ex. 12, p. 575. Hair tests measure exposure to organic mercury, primarily ethyl or methylmercury. The hair closest to the scalp captures the level of mercury in the blood within a month of the time the hair was cut. The remainder of the hair strand provides information regarding historical exposure. Snyder Tr. at 759-60A. Hair mercury levels reflect circulating blood levels of mercury at the time of hair growth, not the level of mercury in tissue (body burden). Snyder Tr. at 761-62.

The April 29, 2000 hair test for mercury demonstrated a low level of mercury in Colten's hair, but one within the reference range of normal for the laboratory, and one well below the 90th percentile for U.S. children ages six to eight. Snyder Tr. at 762-65A; Snyder Pet. Ex. 12, p. 575; Snyder Res. Tr. Ex. 3, p. 4. Although Colten was a little over three years of age at the time of the test, the U.S. norms for older children help to place this result in context.

Given Colten's exposure to mercury through TCVs, Dr. Bradstreet expected this hair mercury level to be higher. He thought the low test results reflected a problem in excreting mercury, rather than low body levels of mercury. Snyder Tr. at 270A-71A. This inverse correlation between hair mercury and mercury body burden was based on Dr. Holmes' work (Cedillo Pet. Ex. 55, Tab X, discussed, *supra*, Section V, Part C.2.c.(3)(b). Snyder Tr. at 247A.

Doctor McCabe disagreed with Dr. Bradstreet, testifying that this result would be expected from Colten's diet (which did not include fish), and from the small amount of thimerosal contained in Colten's vaccines. He also noted that it was consistent with the levels of mercury found in Colten's blood. Snyder Tr. at 763.

(ii) Urine Mercury Levels.

Colten's first urine test for mercury exposure was a post-provocation challenge test conducted on July 21, 2000. Snyder Tr. at 197, 246, 272A. Prior to collecting the urine, Colten was administered 100 mg of DMSA, a chelating agent. *See* Snyder Pet. Ex. 12, p. 544 (upper right corner of report). The results were reported by Doctor's Data laboratory as "very elevated," at 11 µg/g creatinine.[486] *Id*.; Snyder Tr. at 272A-74. Converting this figure to parts per billion (µg/L) would yield a result of 2.2 µg/L of urine. Snyder Tr. at 770-71A. No baseline urinary mercury level was determined before administration of the chelating agent. Snyder Tr. at 274.

However, the reference ranges for this test were based on subjects who were

[486] This test measures a mercury ion in the urine, and is reported as µg/g creatinine, which is a different measurement than µg/L. Snyder Tr. at 770.

not chelated before measurement of their urinary mercury levels. Snyder Pet. Ex. 12, p. 544; Snyder Tr. at 769A, 771A-72. Based on Dr. Woods' research,[487] urinary mercury levels in adults not occupationally exposed to mercury were 3.0 µg/L, pre-chelation; Colten had a lower result, post-chelation. Although the Doctor's Data laboratory reported Colten's results as "very elevated," applying the correct reference range placed Colten's post-chelation mercury level in the range of normal pre-chelation levels. Snyder Tr. at 771A-72.

Doctor McCabe's testimony was also supported by an article filed as Cedillo Res. Ex. L, Tab 5.[488] This study looked at chelation as a method to assess "body burden" of mercury. Healthy adults were tested for mercury levels, and then took a chelating agent. Baseline urinary mercury averaged 2.2 µg/L of mercury. Post-chelation mercury levels were an average of 13.7 µg/L. Based on this small study, Colten's post-chelation mercury level appeared to be low, not elevated. The study also demonstrated why no post-chelation norms have been established for children. One of the 15 adults recruited for this study suffered a serious reaction to the chelating agent, and the study was terminated after only one round of chelation.

A post-chelation urine sample, taken on April 24, 2006, reported that any mercury present was below the detection limit. Snyder Pet. Ex. 12, p. 86. Another post-chelation urine sample, taken on June 26, 2008, was reported by another laboratory as well below the reference range for mercury. *Id.*, p. 70. Another post-chelation urine sample, taken on September 25, 2006, found no detectable mercury. *Id.*, p. 48.

(iii) Blood Mercury Levels.

Colten's blood mercury levels were tested on five occasions, all with findings in the normal range. Snyder Tr. at 757-58. A blood sample drawn on September 21, 2000, was tested for mercury on September 26, 2000. The mercury level of 3 µg/L was well within the reference range. Snyder Pet. Ex. 12, p. 530. Colten's blood mercury levels were measured on December 10, 2004, April 29, 2005, and June 26 and December 11, 2006. All of the results were lower than the reference limit of 10 µg/g,[489]

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[487] Doctor Woods was originally listed by the PSC as an expert witness for petitioners, but he did not file an expert report or testify. *See* Petitioners' Initial Disclosure of Experts, filed February 14, 2006, OAP Master file. His work was relied upon by Dr. Bradstreet. Snyder Tr. at 251-52A.

[488] G. Archbold, *et al.*, *Dimercapto-succinic acid loading test for assessing mercury burden in healthy individuals,* ANN. CLIN. BIOCHEM. 41: 233-36 (2004).

[489] The 10 µg/g level was the upper limit of normal. There was no lower "normal" limit listed.

even though they were all post-chelation tests.[490] The blood mercury levels measured recent exposure, which, in Colten's case, would have been very limited due to his diet and his parents' refusal to administer any additional vaccines. Snyder Tr. at 246-47A, 763.

(iv) Urinary Porphyrin Testing.

According to testing done at the Laboratoire Phillippe August in France, Colten had abnormal urinary porphyrins consistent with mercury exposure. Snyder Tr. at 216. Doctor Bradstreet interpreted Colten's porphyrin test results as consistent with his other observations that Colten demonstrated low levels of thiols, cystine, and glutathione, and he was probably not a good excreter of mercury. Doctor Bradstreet explained that the ratios between certain types of porphyrins were important, and Colten's precoporphyrin level was greater than his uriporphyrin level, an atypical presentation. He based this interpretation on work by Drs. Wood, Nataf, and Geier. Snyder Tr. at 251-52A.

Urinary porphyrin testing represents a "work in progress," according to Dr. McCabe. Precoproporphyrin[491] appears to be a marker of urinary mercury in those occupationally exposed to high levels of elemental or methylmercury, but there is no data on those with intermittent exposure to TCVs. Snyder Tr. at 774-75A; Snyder Res. Ex. T at 5.

Colten's precoproporphyrin test results were somewhat inconsistent. On September 15, 2006, his level was 31.7 nmol. On July 27, 2006, his precoproporphyrin level was 24.6, with a reference range of 2-5. On July 26, 2007, the level had risen to 30, in spite of several rounds of chelation between the latter two tests. Snyder Pet. Exs. 207, pp. 3, 8 and 12, p. 58. These test results conflicted with the urine, hair, and blood tests, all of which showed low or undetectable levels of mercury.

Doctor McCabe noted that Dr. Woods found two porphyrins, precoproporphyrin and pentacarboxyporphyrin, that appeared to equate to other measures of mercury exposure (comparing porphyrins to urinary mercury levels). Colten's urine was high in both. However, Colten was also high in two other porphyrins, heptacarboxyporphyrin and hexacarboxyporphyrin, giving him an unusual profile. Given Colten's many rounds of chelation, Dr. McCabe was highly skeptical that Colten's porphyrin testing represented residual mercury in his body. He noted that Dr. Woods' work demonstrated that chelation lowered urinary precoproporphyrin levels "precipitously."

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[490] The highest blood mercury level was .002 µg/g on December 10, 2004. On April 29, 2005 and on both June 26 and December 11, 2006, Colten's blood mercury was .001 µg/g. Snyder Pet. Ex. 12, pp. 172, 130, 70, and 39.

[491] Precoporphyrin is a different porphyrin than precoproporphyrin. In his testimony, Dr. Bradstreet referred to precoporphyrin to illustrate what he saw as problems in Colten's mercury excretion. *See* Snyder Tr. at 251-53A. Doctor McCabe testified about Colten's precoproporphyrin level in discussing Dr. Woods' pioneering work in porphyrin testing. Snyder Tr. at 774-80A.

Snyder Res. Ex. T at 5; Woods 1996, Snyder Res. Ex. T, Tab 4, at 214.

(f) Measles Virus Antibody Testing.

Measles virus antibody testing measures exposure to measles virus whether from natural infection or from vaccine. A positive test result for measles IgG antibody would be expected in someone who had been vaccinated within the prior two years, and would be indicative of an appropriate immune response to the vaccine. Cedillo Tr. 2781A-82A. From a blood sample drawn on March 8, 2000,[492] Colten tested positive for both measles virus and herpes virus-6 IgG, reflecting his MMR vaccination two years earlier, and some natural exposure to herpes virus.[493] Snyder Tr. at 198, 242A-43A, 371A-72A; Snyder Pet. Ex. 207, p. 1.

However, by March, 2002, Colten did not have detectable levels of antibodies to measles virus, MMR, or herpes virus in his CSF, which Dr. Bradstreet attributed to two years of IVIG treatments. Snyder Tr. at 198. Later, Dr. Bradstreet elaborated on this testimony, stating that the absence of measles virus antibodies in Colten's CSF in 2002, "needs to be interpreted in the light of his previous therapy." Snyder Tr. at 240A. He agreed that most batches of IVIG would have significant levels of anti-measles virus antibodies.[494] Snyder Tr. at 241A.

According to Dr. Ward, Dr. Bradstreet's explanation that IVIG treatments caused the negative result for measles antibodies was not persuasive. If Colten had a persistent measles infection and manufactured antibodies to the measles virus as a result of either that infection or his vaccination, he would not cease manufacturing them simply because he had an IVIG treatment. Snyder Tr. at 947-48A. A negative measles antibody test would be inconsistent with an active, persistent measles infection. Cedillo Tr. at 2787.

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[492] This was also the date of Colten's first IVIG treatment. Snyder Pet. Ex. 12, p. 582; Snyder Tr. at 243A.

[493] For reasons unclear in the record, the sample, collected on March 8, 2000, was not reported as positive until September 24, 2001. This report was not contained in the updated records from Dr. Bradstreet filed in July, 2007, although the report is dated September 24, 2001, and was addressed to Dr. Bradstreet. Snyder Pet. Ex. 207, p. 1. This exhibit was filed on October 26, 2007, shortly before the hearing began.

[494] According to Dr. Ward, the FDA requires that all IVIG formulations contain a minimum level of measles neutralizing antibodies, but the levels vary widely above that amount, depending on the source. If Dr. Bradstreet were using IVIG to treat a persistent measles virus infection, he should have selected the lots containing the highest levels of measles antibodies. Snyder Tr. at 944A-45A. Doctor Bradstreet testified that the titer of anti-measles virus antibody was not a consideration in his selection of IVIG batches. Snyder Tr. at 240A-41A.

(g) Endoscopy and Colonoscopy Results.

In May, 2002, Dr. Kerry Thek performed an upper endoscopy and colonoscopy on Colten for "poor weight gain, weight loss, chronic diarrhea, and emesis." Snyder Pet. Ex. 36, pp. 1, 3. In a letter to Dr. Bradstreet, Dr. Thek noted that Colten had a history of gastrointestinal complaints, including chronic intermittent diarrhea. Her letter also indicated that the pathologist found no colitis or ileitis on the biopsies, but did find several intraepithelial eosinophils in samples taken from Colten's lower esophagus.[495] *Id*., p. 1.

The operative report noted that, on endoscopy, Colten appeared normal from his esophagus through his duodenum. On colonoscopy, Dr. Thek found lymphonodular hyperplasia and ileitis with mild hemorrhage in his terminal ilium. Her assessment was "possible ileitis in terminal ileum," pending biopsy report. Snyder Pet. Ex. 36, p. 3. The pathology report on the endoscopy samples showed several intraepithelial eosinophils; the report on the colonoscopy samples was entirely benign, finding "no significant histopathology." *Id.*, p. 4.

Doctor Bradstreet wanted a second opinion on the biopsy samples and arranged to send the tissue blocks to a Dr. Andrew Anthony. Snyder Tr. at 210. Doctor Anthony's report (Snyder Pet. Tr. Ex. 3)[496] was not filed prior to trial, with the rest of Dr. Bradstreet's records. Doctor Anthony's findings were different from those of the first pathologist. He found more eosinophils in the duodenum. In the terminal ileum, he found "prominent lymphoid tissue" with a hyperplastic follicle with a large germinal center on one sample. He also found two large collections of eosinophils. In the cecum, he found "a mild focal excess of mucosal chronic inflammatory cells with an eosinophil component." He commented that the changes raised "the possibility of an allergic process," and commented that they were "similar to those seen previously in children with autism." Doctor Bradstreet interpreted this pathology report as a "diagnosis of eosinophilic gastroenteritis or enteritis that certainly matches up with his high IgA's and some of his other observations and is consistent with his immune

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[495] In some inflammatory gut diseases, such as ulcerative colitis, eosinophils are found in the gut wall as a result of inflammation. However, intraepithelial eosinophils are not evidence of an inflammatory bowel disease, and are found in developmentally normal children. Increased eosinophils in the gut appear to be a consequence of constipation, with increased inflammation in the gut wall caused by impacted stools. Hazlehurst Tr. at 621A-23A, 628A; Hazlehurst Res. Ex. A, Tab 15, Table 2.

[496] This exhibit is not on letterhead, so there is no indication where Dr. Anthony practiced at the time of the report. Although there is a fax machine header, with a date/time entry (04 Sep 2003) there is no indication who faxed the document, to whom, and from where. The signature block on the report is "Dr Andrew Anthony MRCPath (by published works)" A review of the exhibits filed in the Theory 1 test cases disclosed that Dr. Anthony was a co-author of several of Dr. Wakefield's articles (*see, e.g.*, Snyder Pet. Exs. 120 and 186; Cedillo Pet. Exs. 61, Tab NNN and 63, Tab T; and Cedillo Res. Ex. T, Tab 32. He was one of Dr. Bradstreet's co-authors on the Bradstreet 2004 article, filed as Cedillo Pet. Ex. 61, Tab M. That article listed his position at the Royal Free Hospital in London. Colten's case was one of the three reported in this article. Snyder Tr. at 255.

disregulation. And when combined with the measles virus report from the biopsy, is concerning about the persistence of that virus triggering some of these changes." Snyder Tr. at 211. I note that Colten's IgA levels were never high, and it is likely Dr. Bradstreet simply misspoke, meaning instead Colten's high IgE levels.

(h) Testing for Measles Virus RNA.

Based on reports from Dr. O'Leary's laboratory, Unigenetics, that measles virus had been detected in the gastrointestinal tract of some children with autism, Dr. Bradstreet thought it was logical to confirm his suspicion of a causal relationship between the MMR vaccine and onset of Colten's symptoms. He traveled to Dublin to meet Dr. O'Leary to ask if CSF should be tested for the presence of the measles virus, and to find out whether Unigenetics could detect it, if present. Doctor O'Leary gave him a tour of the laboratory and explained the collection, shipping, and testing procedures. Snyder Tr. at 200-01. He thereafter arranged for Colten's blood, CSF, and gut tissue to be tested for the presence of measles virus RNA. Snyder Tr. at 201-04A.

Colten's CSF and blood samples were drawn in Dr. Bradstreet's office on April 17, 2002, and shipped to Unigenetics. The CSF sample was reported back as positive for measles virus at 3.7×10^4 copies per nanogram of total RNA. Snyder Pet. Ex. 12, p. 419. Colten's blood sample tested negative for the presence of measles virus. *Id*., p. 417 (duplicates of these reports appear at several other places in the record). Both reports were dated June 5, 2002. *Id.*, pp. 417, 419. These reports are what Dr. Rima called "headline reports" in that they simply reported the results without explaining how the copy numbers were computed. *See* Snyder Tr. at 929-30.

A terminal ileal biopsy, collected during Dr. Thek's endoscopy and colonoscopy of Colten on May 30, 2002, was received by Unigenetics on December 12, 2002.[497] It also tested positive for the measles F gene RNA by PCR testing performed by Unigenetics. The copy number was very low, 7 copies per nanogram of total RNA. Snyder Pet. Ex. 12, p. 390. Petitioners' expert, Dr. Kennedy, testified that this result was quite low, and was only comfortable with calling the gut biopsy results "indeterminate."[498] Snyder Tr. at 379A-82A.

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[497] A possible explanation for the delay in sending the biopsy to Unigenetics appears at Snyder Pet. Ex. 12, p. 352, indicating that on December 6, 2002, Dr. Bradstreet discussed Colten's case with Colten's attorney, and would send samples of Colten's CSF and bowel biopsies to either Unigenetics or another laboratory within a week. If a second CSF sample was sent to Unigenetics at the same time as the gut biopsy, there is no record of the results from it.

[498] In testifying in *Cedillo*, Dr. Kennedy reported some concern about Unigenetics' results showing low copy numbers. Cedillo Tr. at 1815-17. In his testimony in this case, he appeared to retreat from his concern about samples with low copy numbers, and suggested that Colten's gut biopsy might be a "low positive," based on his supposition that the blood sample was assayed at the same time as the gut sample. Snyder Tr. at 379A-80A. However, the blood and gut biopsy specimens were tested on different dates and could not have been run concurrently. *See* Snyder Pet. Ex. 12, p. 334 (gut biopsy received on

To Dr. Bradstreet, the positive test result from the CSF sample meant that the virus was reproducing in the brain. Snyder Tr. at 205. Viral replication explained Colten's dependence on IVIG to relieve his autism symptoms and why his symptoms returned when he was withdrawn from IVIG. Snyder Tr. at 205-06.

(i) Other Tests.

Doctor Bradstreet testified that Colten's adenosine deaminase[499] level was high, reflecting immune dysregulation. Although his TNF-α level was reported as normal by the laboratory, and there is a handwritten notation on the laboratory report of "good," Dr. Bradstreet testified that "subsequent literature" indicated it was actually high. Snyder Tr. at 197-98; Snyder Pet. Ex. 12, p. 457. Subsequent testing, on January 12, 2006, showed a normal TNF-α level. Snyder Pet. Ex. 33, p. 7. Doctor Bradstreet also noted that Colten's neopterin[500] levels were high in September, 2006, in spite of the years of IVIG treatment. Snyder Tr. at 216; Snyder Pet. Tr. Ex. 2 at 31; Snyder Pet. Ex. 12, p. 49. Testing in July, 2007, reflected normal neopterin levels. Snyder Pet. Ex. 207, p. 7.

Colten had several antinuclear antibody ["ANA"] tests. This is the primary test used to diagnose systemic lupus erythematosus and other autoimmune diseases. All of the tests were negative. Snyder Pet. Ex. 12, p. 654 (test results from Dr. Otegbeye, noting that "a negative ANA militates against the presence of an autoimmune disease such as SLE"); p. 350 (recording a normal ANA ordered by Colten's allergist); and Snyder Pet. Ex. 33, p. 5 (recording a normal ANA ordered by Dr. Skoda-Smith, an immunologist).

(2) Treatment.

(a) Dietary Supplements.

According to Mrs. Snyder, Dr. Bradstreet recommended various supplements and "de-yeasting." Snyder Tr. at 63. The supplements included CoQ10, flax, SuperNuThera, and others that Mrs. Snyder could not recall. Colten began taking at least some of the recommended supplements almost immediately. Snyder Pet. Ex. 12, pp. 608-09. He did fine on some, but would then "bottom out" and those supplements would be discontinued. Snyder Tr. at 77A.

December 19, 2002 and reported on January 31, 2003) and pp. 417, 419 (CSF and blood received on April 26, 2002, and reported on June 5, 2002). Thus, his stated reason for crediting the low copy number as positive was not supported by the facts.

[499] Adenosine deaminase is an enzyme, low levels of which have been associated with SCID. DORLAND'S at 30.

[500] Neopterin is a compound typically excreted a low levels in the urine. When excreted in elevated levels, it is associated with some malignancies, viral infections, and graft rejection. DORLAND'S at 1228.

Snyder Res. Tr. Ex. 1 contains a list of the dietary supplements Colten received between 1999-2004. Syclovir, a nutritional supplement, was recommended by Dr. Kartzinel, one of Dr. Bradstreet's partners, to treat inflammatory changes in the digestive tract. Snyder Tr. at 230. During cross-examination, Dr. Bradstreet identified some of the other supplements and explained why they were prescribed. He identified alpha lipoic acid as an antioxidant; flax as containing essential fatty acids; and Primal Defense as a probiotic. Snyder Tr. at 232A-33. He explained that NAC was n-acetyl cytine, an orally absorbable form of a thiol amino acid, critical to the development of glutathione, the body's main antioxidant, and one required by the brain. Snyder Tr. at 233. He identified taurine as a neutral amino acid essential for the formation of bile salts, and explained that it had been observed to calm and ease behavioral symptoms. Snyder Tr. at 234A. He indicated that he prescribed it fairly frequently. Without his permission, a company that manufactured it (Kirkman Laboratory) used him as a testimonial for its efficacy. Doctor Bradstreet acknowledged that Kirkman Laboratory was promoting taurine for use in treating autistic patients without any scientific support for the claim, and ran into problems with the FDA as a result. Snyder Tr. at 234A-35A. Colten took taurine for a considerable period of time (*see, e.g.*, Snyder Pet. Ex. 12, pp. 508-09 (December, 2000), p. 522 (October, 2000) and p. 582 (March, 2000)), although laboratory tests in November, 2000, showed that Colten's taurine levels were actually high. Snyder Pet. Ex. 12, p. 515.

The nutritional supplements prescribed by Dr. Bradstreet were also sold by Dr. Bradstreet. His testimony on whether this was a profit-making enterprise was somewhat equivocal. After first testifying that his corporation made "approximately nothing" from the sale of supplements, with "essentially no mark-up at all" (Snyder Tr. at 237A), he gave a nonresponsive answer to the next question, concerning any profit from the sale of dietary supplements. Rather than answering yes or no, he commented that he often "gave supplements away to families in need." Snyder Tr. at 237A.

Colten's experiences with nutritional supplements were not always benign. On October 26, 1999, what appears to be a telephone consultation with a nurse in Dr. Bradstreet's office recorded that Colten was irritable, throwing temper tantrums, not sleeping through the night, and having recurrent diarrhea. Snyder Pet. Ex. 12, p. 601. Colten saw Dr. Sahai that same day. Mrs. Snyder reported that he was having tics at night that Dr. Sahai suspected were myoclonic jerks related to the medications Colten was taking. Doctor Sahai commented that Colten was on "quite a few medications for his pervasive developmental disorder which I am quite unfamiliar with," and suggested they be discontinued. Mrs. Snyder refused, based on the improvement she saw in Colten. Doctor Sahai's observation was that Colten was unchanged neurologically, and still showed signs of a pervasive developmental disorder. Snyder Pet. Ex. 8, p. 8.

Mrs. Snyder frequently commented on problems after the addition of a new supplement. *See, e.g.*, Snyder Pet. Ex. 12, p. 162 (urinary incontinence after adding "mini mineral Ca"). This encounter note indicated that every time Colten was placed on a supplement, he would respond with incontinence or poor behavior; the health care

provider's response was to recommend a decrease in the dose of supplements to one-fourth and to start them one at a time.

(b) Secretin.

Secretin therapy appeared to be the intervention Colten received the longest, beginning on Colten's first visit with Dr. Bradstreet in July, 1999 (Snyder Pet. Ex. 12, p. 608), and continuing through February, 2007 (*id.*, p. 30). He took several forms of secretin, beginning with intravenous secretin, and, in April, 2005, he began to use nasal secretin in combination with intravenous secretin. *Id*., p. 135.

According to Dr. Wiznitzer, secretin does not work as a treatment for autism. Snyder Tr. at 675A. In controlled studies, some children improved while taking secretin, which he attributed to a combination of the placebo effect and the natural history of autism. Secretin might have some positive effect on bowel problems, but not on the core symptoms of autism. Snyder Tr. at 676A-77A.

His testimony was buttressed by Dr. Cook's in *Cedillo.* Doctor Cook testified that he was one of the researchers involved in clinical trials of secretin as a therapy for autism. Three case reports suggested that secretin might be effective, and he was very excited about the prospect of a drug treatment for autism. Secretin was tested against saltwater in a blinded study. The initial data indicated that the children were better after the study. When the study was unblinded, however, those receiving saltwater actually did slightly better than the children receiving secretin. The study itself provided hope to families struggling with this illness, but secretin therapy proved less effective than the placebo. Cedillo Tr. at 1474A-77.

Nevertheless, Mrs. Snyder was adamant that the secretin therapy helped Colten's autistic symptoms, as well as his gastrointestinal ones. She testified that, after beginning secretin, Colten began sleeping through the night. His diarrhea did not entirely go away, but it was much better, and she began to see more eye contact and fewer tantrums. Snyder Tr. at 64-65. Most of Mrs. Snyder's comments in Colten's records about secretin's effectiveness concerned Colten's digestive issues. *See, e.g.*, Snyder Pet. Ex. 12, pp. 294 (stools better formed post-secretin); 173 (secretin helping with bowel formation); 154 (bowels loose; needs Secreflo [secretin]); 138 (stools fine after secretin); 125 (able to tolerate additional fruits and vegetables while on nasal secretin); and 76 (bowels better after secretin infusion). However, she also attributed good behavioral effects to secretin. *See, e.g.*, *id.*, pp. 466 (noting behavioral decline four weeks post-secretin); 432 (sleeping through the night without incontinence when secretin administered every four weeks); 294 (calmer and "more loveable" post-secretin); and 131 (light sensitivity disappeared since starting nasal secretin). Doctor Bradstreet noted in August, 2006, that Colten "seems to require secretin to stay on

target - with it he does very well in school."[501] *Id.,* p. 57.

(c) Chelation.

Doctor McCabe testified no good data demonstrates that chelation therapy works to treat autism. Snyder Tr. at 677A-78A. Nevertheless, approximately 30-40% of Dr. Bradstreet's patients were chelated during his treatment of them, a figure that remained consistent over the five years preceding the hearing. Snyder Tr. at 244-45. Doctor Bradstreet testified that chelation was clinically indicated in patients with a history of significant exposure to a heavy metal; elevated current blood levels of mercury or lead; high levels of porphyrin in the urine, combined with oxidative stress; high hair levels of mercury; or a very strong result to a provocation challenge. Snyder Tr. at 245. He used chelation challenge to diagnose whether a child had excessive levels of mercury, and did not routinely test for mercury or other heavy metals prior to beginning chelation. Snyder Tr. at 245-46. In spite of the fact that none of Colten's tests for mercury was high,[502] and Colten responded poorly to chelation, Dr. Bradstreet ordered numerous rounds of chelation therapy.[503]

Colten was initially chelated with Chemet, the brand name for succimer, or DMSA, in July, 2000.[504] Snyder Tr. at 229-30. Based on the results from this test, Dr. Bradstreet prescribed 100 mg of Chemet to be taken three times a day for three days, followed by an 11 day break, repeated for 10 cycles of chelation. Apparently Dr. Kartzinal reduced the dose by half, to 50 mg of Chemet three times a day, according to nursing notes in the records.[505] Snyder Pet. Ex. 12, p. 543. Although the date Colten began taking Chemet was not recorded, the prescription was dated August 3, 2000, and a message regarding the recommended dosage change was left on August 4, 2000.

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[501] I note that Dr. Bradstreet made virtually identical claims for IVIG's efficacy for Colten. *See* Snyder Pet. Ex. 12, p. 25 ("One of the few things that has ever helped him is IVIG"). In the spring of 2007, Colten scored in the 81st national percentile on reading comprehension and in the 88th for mathematics. Snyder Pet. Ex. 15, p. 29. His most recent IVIG treatment prior to academic testing was December 11, 2006. Snyder Pet. Ex. 12, p. 32.

[502] Colten's urinary mercury test collected on July 21, 2000 (Snyder Pet. Ex. 12, p. 544), was the only mercury test noted by Dr. Bradstreet to be abnormal. Snyder Tr. at 246. Doctor McCabe explained that the post-chelation mercury level found on this test was, in fact, a normal level of mercury, even in an individual not chelated. *See* Part C.3.b.(1)(e), *supra*.

[503] Doctor Bradstreet acknowledged that Colten responded poorly to chelation. Snyder Tr. at 247A-48A.

[504] *See* PDR at 2458.

[505] Nursing notes, dated August 14, 2000, reflected that Colten took the 50 mg dosage. Snyder Pet. Ex. 12, p. 528.

A nursing note reflected that Colten became very agitated and noncompliant five days after chelation, but that his behavior was back to normal by August 14, 2000. On August 16, 2008, Dr. Bradstreet's records reflected that Colten was experiencing myclonic jerks at night. Snyder Pet. Ex. 12, p. 534. Doctor Bradstreet recorded temporary setbacks with the chelation and decreased Colten's dose that same day. *Id*.

The second round of chelation did not go nearly as well. A nurse's note dated August 21, 2000, reflected that, upon restarting the Chemet on August 20, Colten was going "beserck." He was described as aggressive and noncompliant, with repetitive behaviors and tantrums. Snyder Pet. Ex. 12, p. 528.

Nevertheless, another round of chelation began in October, 2000. Chemet was to be compounded "per new chelation protocol," at a dosage of 200 mg, three times a day for three days, followed by an 11 day break, repeating as directed. Snyder Pet. Ex. 12, p. 528.

This round of chelation also did not go well. Colten visited HFHC with complaints of back pain on October 3, 2000, the day after beginning chelation. His primary care provider, Dr. Von Elten, noted that 5% of children taking Chemet developed back or flank pain. Snyder Pet. Ex. 7, pp. 48, 50.

The Snyders called Dr. Bradstreet's office on October 5, 2000, to report that Colten was up all night with high-pitched screaming, and that he was more constipated since the last IVIG treatment. Doctor Bradstreet recommended Epson salt baths and an enema. Snyder Pet. Ex. 12, p. 523. The next day, Dr. Bradstreet asked to see Colten. *Id.* On October 9, 2000, Mrs. Snyder called to report that, since starting glutathione, Colten was vomiting and complaining of a backache. Doctor Bradstreet recommended waiting until Colten was stable before restarting chelation. Snyder Pet. Ex. 12, p. 523.

Colten returned to Dr. Von Elten's office on October 12, 2000, with continuing complaints of back pain. All tests conducted were normal, but Dr. Von Elten wrote: "I am concerned regarding the treatment that he is getting from Dr. Bradstreet that (sic) would like to rule out serious cause for the child's back pain." Snyder Pet. Ex. 7, p. 47. He ordered additional tests, including renal and abdominal ultrasounds. *Id.* Colten's creatinine, sodium, and carbon dioxide levels were low, but the other tests were all normal. *Id*., pp. 43-46.

Colten returned to Dr. Von Elten on October 24, 2000. Mrs. Snyder told Dr. Von Elten that Colten had made a dramatic improvement, reporting that "[h]is personality has come back and he has not complained of back pain since stopping the Chemit (sic)." Doctor Von Elten recommended against restarting Chemet. Snyder Pet. Ex. 7, p. 41.

At Dr. Bradstreet's office three days later, Mrs. Snyder reported that it took a

month to get Colten back to normal after chelation, and that he had been self-injurious, noncompliant, and aggressive. Snyder Pet. Ex. 12, p. 520. However, on November 10, 2000, Mrs. Snyder reported that Colten "did fine while on DMSA, when off is when regression occurred (sic)." Snyder Pet. Ex. 12, p. 513.

Chelation therapy continued in February, 2005, with a prescription for DMPS, another chelating agent.[506] Snyder Pet. Ex. 12, p. 161. He developed incontinence while using DMPS. *Id*., p. 141. In spite of this adverse reaction, another DMPS prescription was written in June, 2005. *Id*., p. 122. This time, reactions included "meltdowns," night sweats, and agitation. *Id*., p. 117. Doctor Bradstreet's physician's assistant ordered a reduction to a half dose of DMPS. *Id.*

Colten began getting an intravenous form of chelation in April, 2006, using a chelator called CaEDTA.[507] Snyder Pet. Ex. 12, pp. 89-92. He received additional treatments of CaEDTA in May and June, 2006. *Id.*, pp. 74, 63. The day after the May chelation, his parents reported that he was easily irritated and having headaches and stomachaches. *Id*., pp. 76-77. Four days after the June chelation, he had headaches and his arms and legs hurt. *Id*., p. 62.

In August, 2006, after Colten's first urinary porphyrin test, Dr. Bradstreet again prescribed DMPS. Snyder Pet. Ex. 12, pp. 56-57. His mother reported that, after three suppositories of DMPS, Colten became incontinent, paranoid of the dark, and easily irritated. She described him as more withdrawn, and said he complained of bone aches, headache, and fatigue. *Id*., pp. 46-47. Colten had another CaEDTA treatment that same day. *Id*., p. 48. This was apparently Colten's last chelation.

Doctor Bradstreet conceded that Colten did not respond well to chelation. Snyder Tr. at 247A-48A. The medical records, including reports from Mrs. Snyder, reflected that Colten did poorly after every round of chelation therapy, although the effects from CaEDTA appeared to be milder than those from DMSA or DMPS. The more disturbing question is why chelation was performed at all, in view of the normal levels of mercury found in the hair, blood, and urine, its apparent lack of efficacy in treating Colten's symptoms, and the adverse side effects it apparently caused.

(d) Immunoglobulin Therapy.

During the course of his treatment by Dr. Bradstreet, Colten received oral

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[506] DMPS is 2,3-dimercaptopropane-1-sulfonate. MED. ABBREV. at 117. Both Dr. Woods and Dr. McCabe called DMPS a highly effective chelator of mercury bound to tissue (body burden). *See* Woods 1996, Snyder Res. Ex. T, Tab 4, at 214 and Snyder Res. Ex. T at 2.

[507] This was apparently calcium edate disodium. MED. ABBREV. at 74. *See* PDR at 1851.

immunoglobulin[508] ["OIG"], intravenous immunoglobulin (Gamunex or Gamimune) ["IVIG"],[509] Baygam, subcutaneous immunoglobulin, and intramuscular gamma globulin ["IMIG"]. Snyder Tr. at 229; Snyder Pet. Exs. 12, pp. 600, 584, 535, 231 and 33, p. 17. Gamunex and Gamimune are brand names for intravenous gammaglobulins. Snyder Tr. at 232A. Baygam is an injectable immunoglobulin. Snyder Tr. at 232A.

Colten actually began immunoglobulin therapy on November 2, 1999, with intramuscular immunoglobulin. Snyder Tr. at 237A, 243A; Snyder Pet. Ex. 12, p. 600. A recent history provided by Mrs. Snyder on the date of his first immunoglobulin treatment noted that Colten's speech was improved and he was using more words. He was jumping and running, and had increased socialization and social functioning. His eye contact was not improved, and he was still banging his head and having some behavioral problems, including more than three weeks of screaming. *Id.,* p. 600. The office notes from Colten's next visit, a month later, reflected similar recent behavior with the exception of increased eye contact. *Id.,* p. 595. He received OIG at this visit as well as IMIG. *Id.*

Sometime in early 2000, Dr. Bradstreet recommended that Colten begin IVIG treatment. *See* Snyder Pet. Ex. 7, p. 54 (note, dated February 11, 2000, involving discussion between Drs. Von Elten and Bradstreet regarding IVIG protocol). The IVIG treatments began on March 8, 2000. Snyder Pet. Ex. 12, pp. 583-87. Doctor Bradstreet noted the earlier discussion with Dr. Von Elten, saying: "We discussed this with the Residency Program at Halifax and all are in agreement to try to help Colten with IVIG to remove the antibodies," referring to the IgE and anti-MBP antibodies. *Id*., p. 583. Reviewing Dr. Von Elten's own notes, this "agreement" with the proposed treatment appears to be an overstatement. *See* Snyder Pet. Ex. 7, pp. 52-54.

At the time Colten's IVIG treatment began, Dr. Bradstreet considered IVIG therapy to be clinically indicated if a patient had evidence of a dysregulated immune system, preferably with evidence of autoantibodies, such as anti-myelin antibodies or anti-endothelial antibodies. Snyder Tr. at 237A-38A. Evidence of immune dysregulation would include IgA deficiencies, subclass IgG and IgM deficiencies, defects in cell-mediated immunity, or autoimmunity. Snyder Tr. at 238A. According to

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[508] Doctor Bradstreet testified that oral immunoglobulin is "essentially pooled human immunoglobulin" for passive immunity. Snyder Tr. at 229.

[509] "IVIG" is intravenous immunoglobulin. MED. ABBREV. at 195. The administration of IVIG, according to Dr. Bradstreet's records, was a time-consuming and labor-intensive process. To illustrate, Colten's 6th IVIG treatment, administered on August 16, 2000, began at 8:30 AM, with application of a topical anesthetic. The IV was established at 9:30 AM, and infusion of Gamimune began at 9:50 AM, followed by SoluMedrol (a steroid), Benadryl (an antihistamine), and Nubain (an opiate pain medication prescribed as a sedative). *See* http://www.fda.gov/medwatch/safety/2003/03apr_pi./nubain_pi.pdf) (;ast visited on February 5, 2009). More Gamimune was administered at 12:30 PM. A nurse noted Colten's condition every 15 minutes, until 3:30 PM, when the IV was discontinued. Snyder Pet. Ex. 12, pp. 533-37.

Dr. Bradstreet, Colten had significant titers of autoantibodies to MBP, a positive rheumatoid factor, IgA deficiency, and very high levels of IgE. Snyder Tr. at 238A-39A. The anti-MBP titer, in the presence of Colten's history and symptoms, was of the greatest concern to Dr. Bradstreet in the decision to begin IVIG therapy. His treatment objective was to improve the child's behavior to the point of recovery or near recovery. Thus, although laboratory values would be monitored, treatment efficacy would be measured by Colten's behavior–in Dr. Bradstreet's words, "what's going on with the patient"–rather than strictly on laboratory values.[510] Snyder Tr. at 239A. Doctor Bradstreet was also concerned about Colten's ongoing gastrointestinal problems, his immunological history, and his regressive history. He believed that Colten had an autoimmune-related encephalopathy, a condition that would benefit from IVIG. Snyder Tr. at 190.

Respondent's experts were highly skeptical of Dr. Bradstreet's treatment rationale and its efficacy. Doctor Zweiman testified that the available studies on IVIG therapy for ASD had such significant design flaws that it was impossible to extrapolate an effect on ASD's core features. He commented that both a group of Canadian experts and the American Academy of Pediatrics have found insufficient data to support the use of IVIG in treating autism. Snyder Tr. at 615A, 678A. In his report, Dr. Zimmerman also noted that there was no evidence that administration of immunoglobulins improved autistic symptoms. Cedillo Res. Ex. FF at 2.

Doctor Ward testified that IVIG is not a treatment commonly used for wild-type measles virus infections[511] and, thus, it was unlikely to be effective in treating a persistent measles infection of any type. Snyder Tr. at 943A-45A. Since Colten was already manufacturing IgG against the measles virus at the time his IVIG treatments began (Snyder Pet. Ex. 207, p. 1), the measles antibodies in the IVIG treatments (Snyder Tr. at 944A) would not do anything his immune system was not already doing.

Both an immunologist and a pediatric neurologist who evaluated Colten in 2005-06 were also skeptical about the IVIG treatments. Doctor Skoda-Smith, an immunologist who evaluated Colten in November, 2005, commented: "I do not know of an immunologist that uses titers of [anti-MBP] antibodies to guide IVIG therapy at this time." She noted that Colten's family attributed his dramatic recovery to the IVIG

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[510] As late as November, 2005, Mrs. Snyder apparently believed that the IVIG treatments were determined, at least in part, on test results for anti-MBP antibodies. *See* Snyder Pet. Ex. 33, p. 15 (Mrs. Snyder stating to Dr. Skoda-Smith that Dr. Bradstreet used MBP titers as a guide to determine when Colten needed another dose of IVIG).

[511] IVIG is used to treat MIBE in rare cases to protect the patient against the disease until immune function is restored or improved. Even then, most of those with MIBE will die unless the underlying and unrelated immunosuppression can be reversed. Snyder Tr. at 945A-46. It is also used on rare occasions with infants whose mothers contract measles in the last few days of pregnancy or shortly after birth. Maternal antibodies against measles commonly protect newborns, but a mother with a recent infection would not have antibodies to pass on to her child. Snyder Tr. at 943A-44A.

therapy and commented: "There are children with poorly described inflammatory diseases of the central nervous system that have responded to IVIG therapy. However, most of these children have some significant marker, physical finding, or neurologic finding related to this underlying inflammation." Snyder Pet. Ex. 33, p. 19. She did not note any such significant marker in Colten. She stated: "I think it would be important for us to find some clear marker that IVIG is benefitting this young man. It is difficult to know without structured or validated behavioral scales, whether we can use behavioral measures alone to guide our therapy in his case." *Id*., p. 20. The pediatric neurologist who examined Colten in January, 2006 (the only time Colten actually saw a pediatric neurologist), commented: "At this time, we have no explanation why these symptoms should be responsive to IVIG. Clearly, his behavioral disturbances are cyclical." *Id*., p. 2. The examiner recommended a referral to a neuropsychologist who specialized in developmental disorders, but the family declined. *Id*. The opinions of both specialists were based on the reports of Colten's family concerning onset, cyclic nature of the symptoms, and efficacy of the IVIG treatments.

Mrs. Snyder testified that prior to Colten's third birthday, there were brief periods when they saw "the old Colten." Snyder Tr. at 64-65. After the IVIG therapy began, Colten's personality "started" to return.[512] His language improved, with parts of words instead of just sounds. Snyder Tr. at 65-66. His facial expressions returned. Although he still engaged in repetitive play, he began responding to his name and interacting with his family. The more he received IVIG, "the more he came back to us." Snyder Tr. at 67. By the time he was in pre-kindergarten, he was doing well. Mrs. Snyder deliberately chose not to tell his pre-kindergarten teacher about his ASD diagnosis, and received good reports from her. Snyder Tr. at 67-68. Mrs. Noonan also testified that after the IVIG therapy began, Colten played better in groups and was more a part of the family. His speech slowly returned. He interacted with her and began to participate in story time. Snyder Tr. at 97-98.

In the medical records, Mrs. Snyder generally noted improvements after IVIG therapy (*see*, *e.g.*, Snyder Pet. Ex. 12, pp. 440, 369), although there were times when the therapy itself (or some component thereof) caused Colten to be ill or to miss school afterwards. *See*, *e.g.*, *id.*, pp. 265, 246, 223, 219, 103. However, she also recorded improvements at the office visits on the date of the IVIG therapy, presumably when Colten's symptoms would have been at their worst. *See*, *e.g.*, *id*., pp. 461, 452, 432. She noted when gaps in the IVIG therapy caused problem behavior. *See*, *e.g*., *id*., p. 406 (about 6 weeks since previous IVIG treatment); p. 335 (Dr. Jekyl and Mr. Hyde at about 16 weeks since the previous IVIG treatment); p. 311 (six weeks since previous

[512] Her statements in the medical records reflected Colten's improvement in September, 1999 (Snyder Pet. Ex. 12, pp. 602-03), a decline in October, 1999 (*id*., p. 601), both negative and positive changes in November, 1999 (increased screaming and head-banging, but more words, better social functioning, and improved motor skills (*id.*, p. 600), improvement in December, 1999 (*id.*, p. 595), worse in January, 2000 (*id*., p. 591), and improvement in February, 2000 (*id*., p. 589). These records preceded the initiation of IVIG therapy.

IVIG); p. 276 (13 weeks since previous IVIG); p. 266 (noting a decline six weeks post-IVIG); p. 256 (noting a decline five weeks post-IVIG). There were times he did well when not receiving IVIG. *See*, *e.g.*, *id.*, p. 383 (August 6, 2002, with previous IVIG on May 6, 2002); p. 235 (doing well seven weeks post IVIG); p. 93 (27 weeks post-IVIG with some minor behavioral issues); and p. 74 (32 weeks post-IVIG and "doing amazingly well").

Doctor Bradstreet could not explain why IVIG therapy was effective in treating Colten, although he had theories. Snyder Tr. at 239A. He testified that IVIG was "an anti-inflammatory," and that it was used in LKS, a condition he described as similar to autism. Snyder Tr. at 240A. He was aware that most batches of IVIG contained anti-measles virus antibodies, but the titers of antibodies in the IVIG he administered were not important to him, as long as the treatment was effective. It was effective in Colten's case, and in the cases of many people with ASD, based on his empirical evidence. Snyder Tr. at 240A-42. According to Dr. Bradstreet, Colten did remarkably well on the treatment, going from severe delay to becoming an A/B student, with excellent language, and a charming and social personality. Snyder Tr. at 190.

In the 2002 time frame, Medicaid withdrew approval for IVIG treatment, so Colten received it less frequently over that period. Both Dr. Bradstreet and Mrs. Snyder reported that if he went longer than 30 days between IVIG treatments, Colten became more irritable, squinted or closed his eyes during conversations, displayed more obsessive behavior, and was less socially interactive. Snyder Tr. at 190-91A. Because Colten regressed when he didn't get IVIG treatments, Dr. Bradstreet concluded that he had immunological dysregulation that was autoimmune in nature. Snyder Tr. at 192. He did not reference any tests objectively measuring autoimmunity in Colten.

During the period from April 29, 2005, to May 19, 2006, the pace of IVIG treatments substantially slowed. Colten had an IVIG treatment on April 29, 2005, a subcutaneous IG treatment on September 15, 2005, a subcutaneous IVIG treatment on October 4, 2005,[513] and an IVIG treatment on May 19, 2006. Snyder Pet. Ex. 12, pp. 131-32, 104-05, and 72-74. In spite of the length of time between the last two treatments, Dr. Bradstreet described Colten as having done "amazingly well." *Id.*, p. 74. During this same time frame, Colten had excellent grades (Snyder Pet. Ex. 7, pp. 10-12), was described as communicating well by both Dr. Evers (*id.*) and Dr. Skoda-Smith (Snyder Pet. Ex. 33, p. 18), and was working above grade level as reflected on the Florida Comprehensive Assessment Test administered in the spring of 2006 (Snyder

[513] There is a prescription for IVIG, dated October 4, 2005 (Snyder Pet. Ex. 12, p. 101) in Dr. Bradstreet's records, and a reference to it at Snyder Pet. Ex. 7, p. 1, but I could find no record showing that either Dr. Bradstreet or Colten's new primary care provider, Dr. Evers, administered it. However, there is a reference by Mrs. Snyder on October 27, 2005, that Colten's last IVIG was administered on October 4, 2005. Snyder Pet. Ex. 12, p. 97. I conclude that the IVIG treatment was actually administered, possibly at home, subcutaneously. *See* Snyder Pet. Ex. 7, p. 22.

Pet. Ex. 15, pp. 35-37). His individual educational program assessment evaluation reported that he was doing well in all academic areas and was loved by many of the students in his regular classroom, but he continued to need remediation and instruction in oral communication (Snyder Pet. Ex. 15, p. 85).

Rather than attributing Colten's obvious improvements in speech, language, socialization, and behavior to the effects of IVIG, secretin, chelation, and/or dietary supplements, Dr. Wiznitzer noted that Colten's developmental pattern was consistent with the natural history of autism in that those with the disorder are at their worst at the second or beginning of the third year of life. Snyder Tr. at 643A. Speech therapy improved his speech, and Colten's normal intelligence permitted him to benefit substantially from speech and language therapy.

D. Expert and Treating Physician Opinions.

1. Doctor Bradstreet's Opinion.

Based on all of the test results, his care and treatment of Colten, and Colten's medical history, Dr. Bradstreet opined that Colten had "measles virus induced encephalopathy from persistence of the measles virus in his CNS."[514] He also opined that Colten had immune dysregulation, presumably secondary to the viral persistence, and caused, in part, by his TCV exposure. Snyder Tr. at 212A. Doctor Bradstreet believed that Colten was still suffering from a chronic encephalopathy at the time of the hearing, although Colten had improved because of the treatment he had provided. Snyder Tr. at 213-14.

He opined that Colten's regression began by May 6, 1998, when he began to become irritable and fussy. Those symptoms, plus the crying and sleep disorder, were all part of his encephalopathic symptoms. Snyder Tr. at 220A-21A. He testified that there was no way to distinguish between these manifestations of ASD and the language regression he later developed. Snyder Tr. at 221A. Doctor Bradstreet did not explain why these symptoms marked the beginning of his encephalopathy, but the earlier and similar symptoms did not.

Based on Mrs. Snyder's reports[515] and his interpretation of Colten's medical

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[514] Doctor Bradstreet believed that vaccines caused between 10-50% of the cases of autism he has treated. Snyder Tr. at 219A-19B.

[515] Although Dr. Bradstreet characterized Mrs. Snyder as an excellent historian regarding Colten's condition (Snyder Tr. at 173A-74), she was reporting events to him that had transpired over a year earlier. I have detailed above my reasons for accepting the contemporaneous medical records as accurate and will not repeat them here. To the extent Dr. Bradstreet's opinions are based on Mrs. Snyder's accounts, they are not reliable. As the Court of Federal Claims has noted, a doctor's "conclusions...are only as good as the reasons and evidence that support them." *Davis v. Sec'y, HHS*, 20 Cl. Ct. 168, 173 (1990). *See also Perreira*, 33 F.3d at 1377 n.6 ("An expert opinion is no better than the soundness of the reasons

records, Dr. Bradstreet opined that Colten's visit to Dr. Sahai on May 6, 1998, was "the first evidence of a low-grade encephalitis condition." Snyder Pet. Ex. 1 at 1. He also opined that Colten had an autoimmune disorder at the time he saw Dr. Otegbeye. *Id*. at 4. He concluded that "Colten Snyder is suffering from what remains a well-described measles phenomena - that being a post-vaccinal encephalopathy." *Id.* at 7. Retreating from the diagnostic conclusion of autism that he reached upon his initial examination of Colten, Dr. Bradstreet went on to say, "we are not speaking of autism, we are describing a post-vaccinal encephalopathy that has some autistic features associated with it." *Id*.

In essence, Dr. Bradstreet presented a theory based on direct and circumstantial evidence. The direct evidence was the presence of measles virus in Colten's CSF and gut, as detected by Unigenetics. The circumstantial evidence was the improvement Colten made based on treatments designed to counter a persistent measles virus infection. He did not identify which of the therapies he provided were specifically targeted toward treating the measles virus persistence. He also failed to explain the relationship, if any, between MBP antibodies and measles virus.

In addition to challenging the scientific bases for, and reliability of, Dr. Bradstreet's opinions, respondent pointed to inconsistencies in Dr. Bradstreet's reasons for therapies and Colten's test results, the scientific evidence concerning the efficacy of such therapies, and challenged his qualifications to offer opinions. Respondent also raised questions concerning Dr. Bradstreet's biases and motives for proffering opinions supporting vaccine causation.

During cross-examination, Dr. Bradstreet identified Colten as one of the three children he described in the article (Bradstreet 2004) that he co-authored with Dr. Wakefield, filed as Snyder Pet. Ex. 188. Colten was identified as Case No. 3 in the article, which indicated that Colten's immune system dysregulation began after the administration of his MMR vaccination. He acknowledged that the conflict of interest statement filed in connection with that article stated that Colten's Vaccine Act claim was filed after the receipt of positive test results for measles virus in his CSF. Colten's petition for compensation was actually filed over a year before the CSF testing was conducted. Snyder Tr. at 255-57A. He acknowledged that at the time he published both his 2003 and 2004 articles, he had two claims, filed on behalf of his son and daughter, pending under the Vaccine Act.[516] He also filed a civil suit against several vaccine manufacturers, a power company, and the American Dental Association, but did not disclose these pending claims or lawsuits in the conflict of interest statements

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supporting it.") (citations omitted).

[516] He later withdrew the claims filed on behalf of his children. Snyder Tr. at 260A.

included in the articles.[517] Snyder Tr. at 259A-60A.

Respondent also explored Dr. Bradstreet's financial motivations for advocating alternative medical treatments for autism. Doctor Bradstreet testified that, over the period of his involvement in Colten's case, he was associated with a number of different corporations or foundations. They included the Autism Research Center, International Autism Resource Center, the International Child Development Resource Center ["ICDRC"], the Good News Doctor, and Creation's Own. The ICDRC is a non-profit corporation. Creation's Own is a for-profit company owned by Dr. Bradstreet. Part of his medical practice is conducted under the auspices of Creation's Own. Snyder Tr. at 235A-37A; *see also* Snyder Pet. Ex. 12, p. 543 (prescription from J. Bradstreet, Autism Research Center). The Good News Doctor is a foundation; the ICDRC is a component of that foundation. The foundation is designed to raise health awareness, foster personal responsibility for health care, and fund health care for the needy. Snyder Tr. at 248A. This foundation raises hundreds of thousands of dollars to care for needy kids, providing them with supplements, medical equipment, and whatever else may be necessary for their treatment. Some of the funds raised also provide for Dr. Bradstreet's treatment or for treatment provided by other physicians. Funds have been provided for endoscopies, for example. Creation's Own corporation received funding from the non-profit ICDRC, meaning that Dr. Bradstreet could directly benefit from medical services paid for by the ministry for some of his 3,000 autism patients. Snyder Tr. at 173A, 249A-50A. When Mrs. Snyder testified that some of Colten's therapy was funded through a ministry, she was referring to the Good News Doctor non-profit corporation. Snyder Tr. at 70, 248A. Colten's medical records also reflected that some of his treatments were funded by the ministry. *See, e.g.*, Snyder Pet. Ex. 12, pp. 1-2; 22, 35, 46, 57, and 590. Respondent also elicited evidence that Dr. Bradstreet sold the nutritional supplements he prescribed or recommended. Snyder Tr. 273A.

Three well-qualified specialists examined Dr. Bradstreet's opinions on the nature of Colten's illnesses, post-vaccination, and all disagreed with his autoimmune reaction/post-vaccinal encephalopathy conclusions.

Doctor Wiznitzer, a pediatric neurologist, noted that the contemporaneous medical records of Colten's hospitalization were inconsistent with an encephalopathy. He pointed out inconsistencies between Dr. Bradstreet's own records of the history of the onset of Colten's symptoms and the facts Dr. Bradstreet cited in his report as evidence of an encephalopathy. Using the contemporaneous records, Dr. Wiznitzer documented evidence of a neurologic examination and nursing assessments describing Colten as alert. Doctor Wiznitzer noted that Dr. Bradstreet's own references did not support his claims. Quoting one of those sources, Dr. Wiznitzer noted that Colten's condition was not "marked by seizures, altered behavior or consciousness, and ataxia," all symptoms common to encephalopathy after measles vaccine. Snyder Res. Ex. A at

[517] The lawsuits were later withdrawn, according to Dr. Bradstreet's testimony. Snyder Tr. at 260A.

3-4.

Doctor Ward, a specialist in infectious diseases with specific expertise in measles virus and vaccine, also noted that Colten received neurologic examinations during his hospitalization, with no indication of any encephalopathic condition, other than the lethargy that prompted the hospitalization,. The lethargy resolved upon rehydration and reduction of his fever. Snyder Res. Ex. K at 5. He found no laboratory evidence of any autoimmune condition or immunosuppression. He noted that Dr. Bradstreet's opinion that Colten's febrile illness "was likely measles" (Snyder Pet. Ex. 18 at 5) was nonsensical, because Colten's white blood cell counts were evidence of a bacterial, not viral infection.[518] Snyder Res. Ex. K at 9.

Doctor Zweiman, an immunologist, opined that Dr. Bradstreet's opinion that Colten had an autoimmune measles encephalitis was unclear, because it was uncertain if he was referring to ADEM (PIEM) or SSPE. In either case, Dr. Zweiman found no clinical support for Dr. Bradstreet's opinion. Snyder Res. Ex. C at 2. Doctor Zweiman found Dr. Bradstreet's reliance on the positive RF test, serum IgA, and anti-MBP tests to be misplaced, as none of these tests were reliable indicators of an autoimmune process or an encephalopathic illness. *Id.* at 2-3. He called Dr. Bradstreet's opinion "seriously flawed" and noted that the evidence Dr. Bradstreet cited in support was either irrelevant or involved wild-type measles infections and an entirely different clinical picture. *Id*. at 4.

I found the opinions of Drs. Ward, Zweiman, and Wiznitzer to be more persuasive than Dr. Bradstreet's. Their opinions are based on Colten's medical records and have the weight of scientific authority behind them.

2. Doctor Kinsbourne's Opinion.

Unlike Dr. Bradstreet, Dr. Kinsbourne did not rely on the theory of mercury dysregulation of Colten's immune system, because, for him, it was unnecessary. Based on the presence of the virus in Colten's system, he opined that Colten's immune system was obviously unable to clear it. Therefore, Dr. Kinsbourne could conclude that the persistent measles virus caused Colten's ASD without determining what allowed or caused the virus to persist. Mercury could be one of those factors, but Colten's inability to mount an appropriate immune response to the MMR vaccine did not depend on any impact of mercury on his immune system. Doctor Kinsbourne also opined that causation in Colten's case did not depend on any form of immune dysregulation predating Colten's vaccination. Snyder Tr. at 486A-87A.

In essence, Dr. Kinsbourne contended that the presence of measles virus in

[518] Doctor Ward also noted that Colten had a very similar white blood cell count during another bacterial infection in March,1999. Snyder Res. Ex. K at 9; Snyder Pet. Ex. 11, p. 18 (blood counts) and p. 16 (bacterial cultures).

Colten's CSF was the medical equivalent of the legal principle *res ipsa loquitur*. If Colten had a neurotropic virus in his CSF and a neurological illness, then the logical connection required by *Althen* was made, and, presumably, the temporal one as well.

According to Dr. Kinsbourne, the measles vaccine caused immune dysregulation,[519] which permitted the virus to persist; the persistent virus caused inflammation in Colten's brain; and the brain inflammation caused Colten's ASD.[520] Snyder Tr. at 488A-89A. Doctor Kinsbourne unequivocally stated that, without the finding of measles vaccine virus material in Colten's system, he would not be able to opine in favor of vaccine causation in Colten's case. Snyder Tr. at 491A. In view of that statement, I defer my conclusion on Dr. Kinsbourne's opinion until after a discussion of the evidence for measles viral material in Colten's CSF.

3. Doctor Kennedy.

Doctor Kennedy offered opinions on measles vaccine causation in this case, as well as opinions on other topics upon which he was not qualified to opine, based on his education, training, and experience. To the extent that Dr. Kennedy offered opinions beyond the scope of his expertise, his testimony is not reliable. *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1268 (Fed. Cir. 2008); *Nimely v. City of New York*, 414 F.3d 381, 399 n.13 (2d Cir. 2005) (stating "it is worth emphasizing that, because a witness qualifies as an expert with respect to certain matters or areas of knowledge, it by no means follows that he or she is qualified to express expert opinions as to other fields."). As he is neither a medical doctor nor a specialist on measles virus, he was not qualified to diagnose Colten's neurological condition (PDD-NOS) as caused by the vaccine strain measles virus.

E. Factual Findings.

1. Autistic Regression.

Although the evidence concerning Colten's language skills prior to and after his MMR vaccination is in conflict, contemporaneous medical records support that Colten's language development arrested, and may have declined, during the two to four months after his vaccination. Mrs. Snyder consistently reported that Colten had between 10-20 words at the time his expressive language skills began to regress in the late spring or summer of 1998, although these reports were all made on or after March, 1999. The video records suggest that Colten's language skills at 13 months were not well-

[519] According to Dr. Kinsbourne, the pharyngitis and recurrent fevers Colten suffered after the MMR vaccine were evidence of the immune suppression caused by the vaccine. Snyder Tr. at 494A, 497A.

[520] A more extensive explanation of Dr. Kinsbourne's theories was set forth and discussed in Section VI.A.2.b.(1) above. Therefore, I have not repeated that explanation here.

developed and Dr. Otgebeye's records document that Colten's vocabulary was underdeveloped when he was 17 months old. The use of just three words at that age was clearly abnormal, but the record does not suggest that he had lost language prior to this visit.

At the time of his MMR vaccination in April, 1998, when Colten was 15 months old, Dr. Sahai noted that there was no evidence of a receptive language disorder. He did not comment on Colten's expressive language abilities. I cannot interpret his lack of comment as reflecting either normal or abnormal expressive language. During the hospitalization, which took place over a month after the vaccination, there were no concerns about Colten's language abilities expressed, either by his parents or by his caregivers. The developmental history indicated that he understood English, was able to express himself, and had an age-appropriate presentation.

The first medical record that suggested Colten's language skills were below normal was that of Dr. Otegbeye, which indicated that Colten had only three words on June 10, 1998, when Colten was 17 months old.

Colten's parents gave various dates for the arrest or decline of Colten's expressive language. In March, 1999, Mr. Snyder provided a history of language loss at 12 months. Mrs. Snyder provided a variety of ages for when the language loss occurred: 15 months and 17 months to Dr. Wenk; 18 months to Dr. Bradstreet; and 19 months at Colten's two year checkup, when she expressed concern about his development.[521]

Although the issue is far from clear, given the range of 12-19 months in parental reports, I adopt the most contemporaneous account of Colten's language problems, and find that Colten's speech problems were first apparent when he was between 17 and 19 months old, or between June and August, 1998. In the following months, his expressive language development plateaued or declined.

Other autistic-like behaviors most likely manifested in the two to three months preceding his two year checkup. In mid-November, 1998, Dr. Sahai described Colten as active, playful, running around, and spitting out a few words. About two and one-half months later, Mrs. Snyder reported behavioral concerns and Dr. Sahai noted some of his own, commenting that Colten's behavior was "unusual." It is certainly possible that Colten's family noticed behavioral concerns earlier than mid-November, 1998, but if they did, they were not sufficiently severe to bring to the attention of Dr. Sahai or his physician's assistant. If they existed in June or July, 1998, it is surprising that the

[521] It is noteworthy that Mrs. Snyder's first recorded account of Colten's language problems did not directly state that he had loss of words. Doctor Sahai recorded Mrs. Snyder as saying "he was speaking relatively well and right around 19 months seemed to just arrest the process." However, the statement "he is no longer speaking well" does suggest some diminution of language or articulation. Snyder Pet. Ex. 8, p. 66.

Snyders did not follow up with Dr. Otegbeye, as they were urged to do. In view of Mrs. Snyder's praise of Dr. Sahai on the initial questionnaire that she completed for Dr. Bradstreet, I expressly reject her testimony that she mentioned Colten's behavior to Dr. Sahai earlier and that he was not responsive to her concerns. In this regard, I note that Dr. Bradstreet was quite critical of Dr. Sahai's care of Colten,[522] and his negative opinions may have influenced Mrs. Snyder's later accounts.

2. Dysregulated Immune System.

Colten's illnesses after his MMR vaccination were of the same type as those that preceded it. The weight loss that prompted, at least in part, Dr. Sahai's referral of Colten to Dr. Otegbeye began between April 7, 1998, and his MMR vaccination. Colten's symptoms and illnesses in the 33 days between his vaccination and his hospitalization were not consistent with a measles virus infection.

The evidence that Colten's immune system was "dysregulated" after his MMR vaccination is unconvincing. No physician, other than Dr. Bradstreet, attributed any clinical significance to the IgA test results obtained by Dr. Otegbeye. Doctor Bradstreet is the only physician who attached any significance to the sedimentation rate or positive RF test results. At best, Dr. Sahai saw the RF test as a reason for another visit to Dr. Otegbeye, a suggestion Colten's parents did not take. Their failure to return to Dr. Otegbeye also suggests that they did not believe Colten's condition was serious.

Doctor Bradstreet's testing showed two results of concern: Colten's extremely high IgG level in July, 1999, and his anti-MBP level in January, 2000. Doctor Zweiman agreed that both of these test results were highly unusual. However, Dr. Bradstreet apparently did not think the IgE level was sufficiently concerning to follow up on it; after noting the result, the next time he mentioned it was when he used it as partial justification for treating Colten with IVIG, seven months later. In view of Colten's numerous food and environmental allergies, the IgE test results likely reflected an overproduction of IgE in response to these stimuli. There was no evidence that a high IgE level is in any way connected with a post-measles vaccine <u>suppressed</u> immune system; indeed, levels that high reflect an <u>over-activated</u> immune response.

The anti-MBP level in 2000 was aberrant in view of the later testing. As Dr. Zweiman testified, anti-MBP testing is difficult to perform; antibody levels fluctuate over time; MBP testing is used primarily for research, not diagnostic purposes; and there is no connection between anti-MBP levels and measles virus infections. The IVIG treatment cannot be responsible for the decline from the initial very high level of anti-MBP, as Colten's anti-MBP level was normal at the time of his first IVIG treatment. His levels remained normal or only slightly elevated throughout the remainder of his treatment by Dr. Bradstreet.

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[522] *See generally,* Snyder Pet. Ex. 1. *But see* Snyder Res. Ex. K at 4-6 (Dr. Ward's assessment of Dr. Sahai's care).

Although Colten's leukocyte levels remained elevated throughout much of his treatment by Dr. Bradstreet, nothing in Dr. Bradstreet's records or testimony indicated that Colten's treatment or diagnosis was predicated on the leukocytosis.

3. Mercury Efflux Disorder.

There is no evidence that Colten suffered from a mercury efflux disorder. The evidence overwhelmingly establish that Colten's mercury level was normal at the time it was first measured, and at an appropriate and expected level, in view of his TCV exposure and dietary history. He responded to his first chelation by excreting mercury in an amount Dr. Bradstreet considered abnormal based on pre-chelation norms. I accept Dr. McCabe's testimony that this level was not abnormal post-chelation. In view of Colten's normal mercury levels on all subsequent tests commonly accepted to measure mercury (hair, blood, and urine), and the conflicts between Dr. Nataf's interpretations of Colten's porphyrin testing and the porphyrin testing research conducted by Dr. Wood, plus Dr. McCabe's testimony that the relationship between urinary porphyrins and mercury body burden is "a work in progress," I find that the porphyrin test results for Colten are too speculative to demonstrate any "mercury effect" in him.

4. Autistic Enterocolitis.

Petitioners have not demonstrated that "autistic enterocolitis" is a diagnosis recognized in the relevant medical community. Even if it were, the evidence that Colten fit the "autistic enterocolitis phenotype" is weak. It is clear from the records that Colten had numerous, and generally mild, digestive system problems from early infancy onward. The medical records do not demonstrate that Colten suffered from chronic diarrhea between his MMR vaccination and his two year well-child visit, with only one mention of "loose stools" beginning on the day of that visit.

After two years of age, Colten had only four or five bouts of diarrhea lasting more than a day or two that were unaccompanied by clear evidence of illness. Mrs. Snyder described three weeks of loose stools in May, 1999, in the questionnaire she completed for Dr. Bradstreet. Thereafter, the parent evaluation sheets, completed prior to most of Colten's examinations by Dr. Bradstreet, provide an excellent record of the condition of his bowels.

Colten had diarrhea in late October-early November, 1999, with no evidence of illness, but it began after he finished taking Diflucan, prescribed to treat a yeast overgrowth in his digestive tract. He was back to normal by early December, 1999. Snyder Pet. Ex. 12, pp. 595, 600-01. He had another bout of diarrhea in mid-January to early February, 2000. *Id*., p. 591. In March, 2002, he had diarrhea again, but it was in conjunction with a febrile illness. *Id.*, p. 432. In May, 2002, Colten began another bout of diarrhea, accompanied by lethargy, resulting in his referral to Dr. Thek. The illness continued into June, 2002. *Id*., pp. 389, 395, and 406. In February, 2003, Mrs.

Snyder described a few episodes of diarrhea. In March, 2003, he had one week of diarrhea. *Id.*, pp. 335, 304. He had problems again in July, 2004, which Mrs. Snyder attributed to some dietary supplements. *Id.*, p. 194.

Although Dr. Thek's history described intermittent, chronic diarrhea, it does not appear from Colten's medical records that the problem was very frequent or severe except during the period May-June, 2002, when his endoscopy and colonoscopy were performed. The descriptions of Colten's bowel habits do not support the descriptions of the children with the purported "autistic enterocolitis" phenotype. Colten's many food and environmental allergies, coupled with occasional viral or bacterial gastrointestinal infections, appear to be a more likely explanation for his symptoms. Contrary to Dr. Bradstreet's records, there is no evidence that Colten had inflammatory bowel disease or enterocolitis. Doctor Thek did not diagnose him with enterocolitis or colitis; from the evidence, Dr. Anthony does not appear to be a physician, and thus could not make such a diagnosis.

5. Measles Infection.

a. Initial "Vaccine Reaction."

Mrs. Snyder attributed Colten's symptoms between his MMR vaccination on April 23, 1998, and his May 26, 1998 hospitalization, to a reaction to the MMR vaccination. Doctor Kinsbourne attributed the illnesses he had, spanning the two or three month period after his vaccination, to the MMR vaccine. Snyder Tr. at 459A-60A.

However, Colten's symptoms were not consistent with such a reaction or with a measles viral infection.[523] The small white patchy exudates in his throat were unlikely to be Koplik's spots, not only because the vaccine virus does not produce Koplik's spots, but also because they were described in the same terms Dr. Sahai applied to their pre-vaccination manifestation. Snyder Tr. at 970A-74.

Measles infections do not generally involve sore throats or pharyngitis. Snyder Tr. at 972-74. Likewise, Colten's other symptoms, between his MMR vaccination in April and his hospitalization in May, were not consistent with measles infection, measles

[523] Doctor Skoda-Smith wrote about the striking timing between Colten's MMR vaccination and the onset of certain symptoms, commenting that they appeared to be related to a post-MMR reaction. Snyder Pet. Ex. 33, p. 18. However, her comment was based on an incorrect history of the timing and nature of the subsequent symptoms. She did not have access to most of Colten's records, particularly those between April, 1998 - January, 2000. Therefore, I attach no weight to these comments. When an expert's opinion is based upon facts not established by the record, a fact-finder may reject the expert's opinion. *Bradley*, 991 F.2d at 1574.

encephalitis (ADEM or PIEM),[524] nor with any other condition known to be associated with measles virus. Snyder Tr. at 971A-74.

Further, the serology testing indicated a high likelihood that a bacterial, not a viral, infection caused the illness that led to his hospitalization. Snyder Tr. at 971-74. Because there is no credible evidence that measles vaccine virus increases the likelihood of other childhood illnesses within 45-60 days of vaccination, I cannot attribute either the illness that led to his hospitalization or his June, 1999 illness to the MMR vaccination.

These factual findings seriously undercut Dr. Kinsbourne's opinions regarding the temporal relationship between vaccination and onset of ASD symptoms in Colten's case.[525] Nevertheless, because the postulated mechanism of injury is a persistent measles virus, it is necessary to consider the evidence regarding measles virus persistence in Colten.

b. Persistent Measles Infection.

Colten's condition between vaccination and the hearing was entirely inconsistent with what is known and generally accepted about measles virus persistence in humans. Doctor Kinsbourne's contrary opinion, ascribing Colten's condition to a persistent measles virus infection, is predicated on, in general, Unigenetics' reports showing the presence of measles virus F gene RNA in children with ASD, and in Colten's specific case, the Unigenetics' reports of measles virus F gene RNA in Colten's gut tissue and CSF. Without these results from Unigenetics, Dr. Kinsbourne was unwilling to opine in favor of vaccine causation of Colten's condition. Snyder Tr. at 491A, 510A, 535A, 539A.

The Unigenetics laboratory reports, which appear at Snyder Pet. Ex. 12, pp. 390 and 419, reflected positive results for measles virus RNA in Colten's terminal ilium (*id*., p. 380) and CSF (*id*., p. 419). If reliable, the report of measles virus RNA in Colten's CSF would be strongly probative that there was an ongoing persistent measles infection in Colten's brain. If reliable, the report of measles virus RNA in Colten's gut would be probative of the "autistic enterocolitis" disease process proposed by Dr. Wakefield, and the gut-brain connection would provide the linkage between measles virus persisting in

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[524] In his expert reports, Dr. Bradstreet opined that Colten suffered a post-vaccinal encephalopathy. *See, e. g.*, Snyder Pet. Ex. 1, p. 7. In PIEM occurring after measles infection, no measles virus has been found in the brain. Snyder Tr. at 836A. Doctor Ward offered convincing evidence that Colten did not have a post-vaccinal encephalopathy. Snyder Tr. at 971-74; Snyder Res. Ex. K at 11-12. Doctor Wiznitzer came to a similar conclusion. Snyder Res. Ex. A at 3-4 (pages unnumbered in filed exhibit). I note that Dr. Kinsbourne did not offer testimony in support of Dr. Bradstreet's opinion.

[525] It appears that Dr. Kinsbourne placed more reliance on Mrs. Snyder's testimony than on the contemporaneous medical records. For the reasons noted above, I found the contemporaneous records to be more reliable. *See Bradley*, 991 F.2d at 1574.

the gut and neurologic dysfunctions manifesting as autism. The Unigenetics laboratory report appearing at Snyder Pet. Ex. 12, p. 417, reflected that Unigenetics was unable to detect measles virus in Colten's peripheral blood.

(1) Irreconcilable Conflicts in Unigenetics' Test Results.

Even if all three test results are accepted as probative and reliable evidence, there is a serious conflict among them. There is no biologically plausible explanation for Colten's blood to test negative, the gut biopsy to test positive at a very low copy number (or, as Dr. Kennedy called it, "indeterminate"(Snyder Tr. at 380A)),[526] and his CSF to test positive for a very high level of the virus.

Doctor Rima explained that because measles is an entirely cell-associated virus, the F gene reported as present in Colten's CSF must have come from cells in the CSF. Snyder Tr. at 881A. Doctor Ward concurred, noting that measles virus has not been isolated from plasma, only from cells. The only cells in the CSF are lymphoid (white blood) cells, the same white blood cells circulating in the blood. Snyder Tr. at 950-51A. Assuming a long-term, persistent measles infection, measles-infected cells in the CSF are inconsistent with the PBMCs having no detectible virus. Snyder Tr. at 881A-82A. If there were high levels of infection in the white blood cells of the brain, it is logically inconsistent that the virus would be absent from the white blood cells in the peripheral circulatory system. Snyder Tr. at 950-51A.

(2) Unigenetics' Results are Unreliable as Evidence.

I conclude that none of the Unigenetics' test results in Colten's case are sufficiently reliable to be considered as probative evidence because of the myriad flaws in Unigenetics' testing. I base this conclusion on the general causation evidence already discussed with regard to Unigenetics, and on evidence specific to Colten's case. Even without considering any of the evidence derived from the U.K. litigation, I nevertheless conclude that the results from these tests are not reliable evidence that Colten had a persistent measles infection.

(a) Inconsistencies with Other Laboratory Evidence.

If measles virus is persisting in the central nervous system of an individual, there

[526] Doctor Kennedy's testimony regarding the gut biopsy's RNA results was highly equivocal. He testified that the gut biopsy "might be a low positive." Snyder Tr. at 380A. Later, he stated that the only site of measles virus that he was concerned about in Colten was his CSF. Snyder Tr. at 382A. Based on his tone and demeanor at the time he offered this testimony, I interpret "concerned about" to mean that this was the test result upon which Dr. Kennedy was relying for his opinions. Testimony by Dr. Rima disclosed that the reported result for the gut biopsy was not a standard quantification report, even for Unigenetics. The report used the ">" sign before the amount. Read literally, this report indicated that there was measles virus F gene present in some amount greater than 7 copies per nanogram of total RNA. Snyder Tr. at 891A.

should be evidence of an enhanced immune response against that virus. Snyder Tr. at 593A; Cedillo Res. Ex. R at 7. Colten had appropriate evidence of measles virus antibodies in his serum nearly two years after the vaccination (Snyder Pet. Ex. 207, p. 1). Nearly four years after administration of the MMR vaccine, in a sample drawn at the same time as the CSF sample that Unigenetics tested for the measles virus RNA, there was no evidence of measles virus. This is inconsistent with an active viral infection. There was no evidence of MMR antibodies in his CSF, also inconsistent with an active viral infection, particularly since Colten demonstrated a previous response to the vaccine in his positive measles IgG titer.[527] Snyder Tr. at 593, Snyder Pet. Ex. 207, p. 2; Snyder Pet. Ex. 12, p. 419.

Measles virus, like other RNA viruses, must replicate constantly in order to survive. Snyder Tr. at 837A-38A. If no antibodies are present to fight the virus, it can replicate virtually unchecked. Thus, if measles virus were actually present in Colten's brain, but he was not manufacturing any antibodies against it, the results would be incompatible with Colten's continued life or health. Since Colten had serum antibodies to measles virus at an earlier point, he was capable of mounting an immune response. If he had measles virus present in his brain, antibodies to the virus would be present. In SSPE, when measles virus persists in the brain, measles antibody levels are extremely high.[528] Snyder Tr. at 841A-42A.

If measles virus were found in the CSF, changes on EEGs or other scans would be expected. Cedillo Tr. at 2855. Colten's 2002 EEG was read as normal. Snyder Pet. Ex. 12, p. 315.

(b) Amount of RNA Detected Is Implausible.[529]

Another highly compelling reason to doubt the validity of the Unigenetics test results for measles RNA in Colten's CSF is the extremely high copy numbers of the virus purportedly found. Doctor Rima echoed the testimony of Dr. Griffin in the *Cedillo*

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[527] In other words, Colten's adaptive immune system had previously fought the virus and produced memory cells (as indicated by the positive IgG titer) capable of recognizing the virus again.

[528] The same is not true in MIBE. *See* Bitnum, Cedillo Pet. Ex. 61, Tab K. However, MIBE occurs only in individuals who were immunosuppressed at the time the virus is contracted or the vaccine was administered. With the possible exception of Dr. Kennedy, all of petitioners' expert witnesses were in agreement that Colten's immune system was functioning when his MMR vaccine was administered.

[529] In interpreting the transcript references to copy numbers, I note that, for reasons unknown, even the corrected transcript in this case perpetuated the error in the earlier version, in that figures referring to exponents are not typed with superscript. For example, in the first paragraph appearing in the Snyder transcript at p. 887A, the figure 104 should have been typed as 10^4; the figure 103 should have been 10^3; and the figure 107 should have been 10^7.

trial about the significance of extremely high copy numbers,[530] saying that they were not biologically plausible. Cedillo Tr. at 2783-84; Snyder Tr. at 930A-31A.

By way of background, Dr. Rima explained that a cell normally has about 200,000 copies of mRNA.[531] If he attempted to grow his best-growing strain of measles virus in Vero cells,[532] at best, he could get 3,000 copies of the measles F gene mRNA per cell. An infected cell would also have 20,000 copies of the measles N gene mRNA, plus some amount of mRNA from the other measles genes present. Based on the level of virus reported in Colten's cells, every cell present in his CSF would have to be stuffed with measles virus. Snyder Tr. at 882A-83A. That would leave no room for the cells' own mRNA. Snyder Tr. at 883A-84A. There would be no need to use PCR testing to detect the virus because it could easily be isolated from the cells or picked up by immunocytochemistry. Snyder Tr. at 884A.

In Colten's case, the figure reported for his CSF was positive at 3.7×10^4 per nanogram of RNA.[533] This meant that Colten had 3,400 copies of the measles virus F gene per cell in his CSF, a result too high to be credible. Snyder Tr. at 929-32A.

(c) The Lack of Backup Data for the Headline Report.

Most laboratory reports in Vaccine Act cases are accepted at face value, although there is no statutory requirement that special masters do so. See § 300aa-13(b)(1) ("test result" among the medical evidence not binding on a special master). If a report reflects the presence of a pathogen, the special master commonly accepts that report as solid evidence that the pathogen is present. However, these laboratory reports come, almost invariably, from certified laboratories. They are produced, to use the terminology found in Federal Rule of Evidence 803(6), in the course of a regularly

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[530] Michelle Cedillo's gut biopsy material was also tested for measles virus by Unigenetics, with a result of measles virus F gene present at 1.67×10^5 copies per ng (nanogram) of total RNA. Cedillo Tr. at 1960-62.

[531] He noted that the manufacturer of the TaqMan kits used a standard figure of about 200,000 copies of mRNA molecules per cell. About 1,000 of those 200,000 copies are GAPDH. Snyder Tr. at 874-75A.

[532] Vero cells have no innate immunity, and thus do not impede viral growth by immune attack. Snyder Tr. at 932A.

[533] Doctor Rima explained that sometimes Unigenetics reported the number of copies of RNA found, and sometimes reported the number of copies per nanogram of RNA. In the latter case, an additional computation was made. Snyder Tr. at 850A. The 3.7×10^4 figure reported for Colten is the equivalent of 37,000 copies of measles F gene per nanogram of RNA.

conducted activity.[534] However, Unigenetics existed for one purpose–to test patient samples for use in litigation.

Test results from hospital or independent laboratories are generally reported in a "headline" form, and are accepted in that form. That is, the laboratory report reflects the test performed and the results therefrom, compared to established normal values, without reference to any underlying data concerning the manner in which the testing was performed.

Doctor Rima raised concerns about Unigenetics "headline" report for measles virus in Colten's case based on the specific amount reported for Colten being biologically implausible, and upon other publicly reported data in the Uhlmann and Bradstreet 2004 papers. He explained that the CSF results reported by Unigenetics for the three children in Dr. Bradstreet's 2004 paper were all scientifically implausible because the amounts of F gene reported were simply too high to be believed. Colten, Child 3, in Dr. Bradstreet's study (Snyder Tr. at 255), had the lowest of the three amounts reported; the measles RNA results for the other two children exceeded the amount of total RNA present in cells. Snyder Tr. at 882A-84A, 890A-94A, 931A. A test that produces impossible results should not be relied upon, and certainly should not be accepted at face value. Even if test results are, in the normal course of business, presumed to be valid, Dr. Rima's testimony shifted the burden of establishing the validity of Unigenetics' results back to petitioners. They failed to convince me that Unigenetics' test results were reliable.

(3) Matters Derived from the U.K. Litigation.

(a) Copy Number Discrepancies.

In the U.K. litigation, Dr. Rima had access to both the headline reports and the underlying data for those reports. The underlying data included the CT number, RNA extraction data, the CT for the GAPDH in the same run, the results for the known positive and negative standards, the actual copy number[535] and information concerning other samples in the same run. Snyder Tr. at 850A. In Colten's case, Dr. Rima had none of that background data to examine.

There were several discrepancies in the way Unigenetics reported their copy

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[534] This reference to Fed.R.Evid. 803(6) does not imply that I applied the rules of evidence to determine any fact in issue in this case, to include determining the reliability of Unigenetics testing. Rather, looking to the reason behind this exception to the hearsay rule, laboratory reports have indicia of reliability. Those indicia are lacking in Unigenetics' results.

[535] The actual copy number is different from the reported copy number. The reported copy number, 3.7×10^4 copies per nanogram of total RNA, is a figure derived from dividing the actual copy number by the amount of mRNA in the GAPDH housekeeping gene in the same sample volume. Snyder Tr. at 869A-72A.

numbers. The most disturbing one was the way Unigenetics handled discordant results. If one run showed a result of zero and the next run of the same sample showed a result of 2,400, Unigenetics would report the sample as positive at 2,400 copies. This happened frequently. Doctor Rima called this reporting method bad science. Snyder Tr. at 865A.

His experience in reviewing the background data at Unigenetics demonstrated that many of the high reported headline figures were the result of low copy numbers of both the targeted substance and GAPDH. Further, many of the copy numbers fell outside the bottom range of the standard curve Unigenetics developed. Snyder Tr. at 878A. Doctor Rima pointed to many examples of this practice in Table 3, Section B, of his report to the U.K. court, filed as Snyder Res. Ex. S at 15-17.

If the standard curve was determined by using 50, 500, 5,000, 50,000, 500,000, and 5,000,000 copies of the known target, with the copies determined based on runs performed on dilutions of the known target, the unknown samples should test between 50 and 5,000,000 for a valid quantification to be made. Most of Unigenetics' samples fell below the lowest number on their standard curve, and any copy numbers reported would be based on an extrapolation. Doctor Rima called this a "deplorable way of doing a test." Snyder Tr. at 873A-74.

The same headline figure could be derived from several different sets of data, but it is dependent on the copy number from the run and the copy number of GAPDH in the sample. For example, the 167,000 figure reported for Michelle Cedillo's sample could have been based on 167,000 copies of the F gene and 100,000 copies of GAPDH. It could also have been based on a run showing 1.67 million copies of the F gene, and 1,000,000 copies of GAPDH, or on a run showing 167 copies of the F gene and 100 copies of GAPDH, since the figure reported is determined by dividing the F gene copy number by the GAPDH copy number. Snyder Tr. at 875A-76A. The "per nanogram of total RNA" is based on the fact that 100,000 copies of GAPDH is the equivalent of a nanogram of RNA. Snyder Tr. at 874-75A.

Without the underlying data, it is impossible to determine how the headline figure reported by Unigenetics was derived. High copy numbers were not necessarily the result of low CTs; high copy numbers did not necessarily imply a large quantity of the target substance in the sample amplified. Snyder Tr. at 876A-77A. In Colten's case, no data on the number of copies was produced. Snyder Tr. at 877A-88A.

(b) Bradstreet 2004 Paper and U.K. Litigation Data.

Doctor Rima illustrated some of the problems in Unigenetics' reporting, using Dr. Bradstreet's 2004 paper, Snyder Pet. Ex. 188. Data from Table 2, Snyder Pet. Ex. 188, p. 42, was reproduced on slide 8, Snyder Res. Tr. Ex. 4. Snyder Tr. at 884A. Based on Dr. Rima's access to the U.K. litigation data, he was able to find backup data concerning the other two children upon whom Dr. Bradstreet's paper was based, but

not Colten's data. The additional information concerning Child 1 and Child 2 in Dr. Bradstreet's article appeared on slide 8, with their numbers from the U.K. litigation materials (with Child 1 appearing as number 490 and Child 2 as number 265 on Dr. Rima's slide 8). Snyder Tr. at 885-86A.

Child 1 in Dr. Bradstreet's article (Child 490 on Dr. Rima's slide) had 2.42×10^7 copies of measles virus F gene per nanogram of total RNA.[536] That result meant that every bit of mRNA in that child's CSF cells was measles F gene, with no room left for anything else, not even the other mRNA necessary for cells to live and function. Doctor Rima called this "completely and utterly implausible." Snyder Tr. at 886A-87A. The result for Child 2 (in Dr. Bradstreet's article), who was Child 265 on Dr. Rima's slide, had similarly high, and equally implausible, copies of measles virus F gene per nanogram. Snyder Tr. at 887A-89.

Doctor Rima's chart (slide 8) showed the actual figures for GAPDH and F gene copies from which the headline figures reported by Dr. Bradstreet were derived. In both cases, the GADPH amounts were extremely low, which is what would be expected in CSF since the cell counts are low in CSF. Based on the method for computing the headline results, a low denominator (the GAPDH count) guaranteed a high result for the headline figure. In Colten's case, given the type of material being tested, it is reasonable to infer that the cell count, and hence the GAPDH count, would be low.

Allelic discrimination tests were run a year later on the CSF samples from Child 1 and Child 2. Both tested negative for measles virus in the CSF. Snyder Tr. at 902. Based on all the evidence he had access to from the U.K. litigation, Dr. Rima concluded that any RNA in the CSF of these two children was based on contamination. Snyder Tr. at 903.

Doctor Rima noted that Dr. Bradstreet's 2004 article referenced information not contained in Colten's headline report, indicating that measles nucleocapsid protein was found in the three cases. Doctor Rima did not know where this information came from, but noted that he found no evidence regarding testing for measles virus proteins in the material he examined for the U.K. litigation. Snyder Tr. at 893-94A.

Another criticism of Dr. Bradstreet's research was voiced by Dr. Ward in testimony in *Cedillo*. In persistent measles brain infection (SSPE), there is a pattern of higher antibody titers in CSF than in blood. In Dr. Bradstreet's research, the measles antibody levels were lower in the CSF than in the blood, which would tend to indicate there was no persistent brain infection by the vaccine strain measles virus. Cedillo Tr. at 1831-32.

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[536] Simple mathematics proves Dr. Rima's point. Converting the reported figure of 2.42×10^7 results in 24,200,000 copies of the measles F gene per nanogram of total RNA. The total amount of all mRNA in a cell is only 200,000 copies.

F. Applying *Althen.*

In their post-hearing brief, petitioners acknowledged their burden to establish each of *Althen's* three factors by a preponderance of the evidence. Sndyer Pet. Post-Hearing Br. at 2, 7. Petitioners incorporated by reference the legal arguments concerning what constitutes proof of the *Althen* factors from the post-hearing briefs filed in *Cedillo* (pp. 172-187) and *Hazlehurst* (pp. 2-6). Snyder Pet. Post-Hearing Br. at 9. Petitioners correctly noted that scientific certainty regarding causation is not required by the Vaccine Act, and that a showing that a vaccine was a substantial factor in causing the injury is sufficient. Snyder Pet. Post-Hearing Br. at 7.

In the Cedillo Pet. Post-Hearing Br. at 184, incorporated by reference in the instant case, petitioners attempted to reformulate the *Althen* test. They argued that a showing that a petitioner: "(1) was healthy (or more healthy); (2) received a covered vaccine; and (3) subsequently suffered an injury that, in theory can be caused by the vaccine; and (4) experienced the onset of symptoms within an appropriate time after the vaccine" was held to be sufficient evidence of causation in a number of cited cases, and therefore obliquely argued that this should be the test for causation. This reformulation neglects to include the statutory requirement that a petitioner demonstrate "by a preponderance of the evidence" that the injury in question was caused by the vaccine (§ 300aa-13(a)(1) (emphasis added)), a standard the special masters found to be met in those cited cases.

In the Cedillo Pet. Post-Hearing Br. at 172, petitioners suggested that the "standard of proof" is relaxed in Vaccine Act cases. In Vaccine Act cases the standards of admissibility are relaxed, in that the technical rules of evidence do not apply. *See* § 300aa-12(d)(2)(b) ("flexible and informal standards of admissibility of evidence" to be used). The difference between "standards of proof" and "standards of admissibility" may be simply one of semantics, or petitioners' choice of wording may be deliberate. The Vaccine Act requires petitioners to prove their case by the preponderance of the evidence. § 300aa-13(a)(1). That proof may be adduced by less formal processes and relaxed standards for admissibility of evidence.

The preponderance of the evidence standard in Vaccine Act cases involving an off-Table injury is the same standard ordinarily used in tort litigation. *Hines*, 940 F.2d at 1525; *Althen*, 418 F.3d at 1278. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. What is different in Vaccine Act cases, and one of the reasons proof of actual causation is easier for petitioners under the Vaccine Act, even in off-Table cases, than in traditional civil litigation, is that the methods of proof are relaxed, in that the rules of evidence do not apply, and petitioners need not establish negligence, defective design, manufacturing flaws, or, indeed, any tort cause of action, merely cause of injury. *See* § 300aa-12(d)(2).

The *Althen* factors provide the framework for determining if petitioners have met

their burden to demonstrate that a vaccine caused the injury claimed.

1. Medical Theory.

Althen requires more than merely a medical theory. Petitioners must offer a biologically plausible medical theory. *See Walther v. Sec'y, HHS*, 485 F.3d 1146, 1148 (Fed Cir. 2007) and *Pafford*, 451 F.3d at 1355-56 (Fed. Cir. 2006) (petitioner's theory must be reputable). The theory of measles virus causation is neither biologically plausible nor reputable, in view of all that is known about measles viral infections of the brain. Not a single measles virologist came forward to testify on behalf of petitioners. Every measles virologist who testified stated that the theory advanced by petitioners flew in the face of decades of research and clinical experience with both the wild-type and vaccine strains of the virus.

Doctor Griffin did not consider the theory that the measles vaccine virus persisted and caused disease in both the gut and the brain to be biologically plausible. Cedillo Tr. at 2795A-96. What measles virus does when it enters the brain is well-known, and it does not produce symptoms or damage consistent with autism. Cedillo Tr. at 2796-97.

Petitioners correctly noted that the medical theory proffered to explain how a vaccine could cause an injury need not be one recognized by the general scientific community, supported by epidemiologic studies, or identified by a pathologic marker. In their view, a theory is sufficient, if "supported by competent evidence." Snyder Pet. Post-Hearing Br. at 7-8 (emphasis added), citing *Capizzano* and *Knudsen*. "Competent" was not defined by petitioners. What is missing from petitioners' formulation of the medical theory prong of *Althen* is the requirement that such a theory be reliable. *See Knudsen*, 35 F.3d at 548.

Under the Vaccine Act, a special master may determine the reliability of a medical theory by considering the framework established by *Daubert*. *See Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999) (framework established by *Daubert* for evaluating the reliability of evidence appropriate for use by special masters).

Daubert requires that an opinion be supported by something more than subjective belief; it must be grounded "in the methods and procedures of science." A non-exclusive list of factors to be considered in evaluating an expert's opinion are: (1) whether the theory is generally accepted in the scientific community; (2) whether it has been subjected to peer review and publication; (3) whether it can be or has been tested; (4) and whether the known potential error rate is acceptable. *Kumho Tire*, 526 U.S. at 149-50.

It is clear that petitioners' theory is not generally accepted. There was no evidence that the measles virus could cause ASD, only speculation that it might. There are no articles supporting Dr. Kinsbourne's theory that persistent measles virus causes

brain inflammation of the type seen in ASD brain pathophysiology. At best, there is some evidence of an ongoing inflammatory process in ASD, but no indication that it is virally-caused. The excitation-inhibition theory is likewise unsupported in the peer reviewed medical literature; at best, there is some speculation that some ASD symptoms may be a reflection of an excitatory-inhibitory imbalance. And as for the MINE theory, it has not been subject to peer review, and after Dr. Dyken's editorial, has apparently never again resurfaced in the medical or scientific literature.

The theory rests on one key piece of evidence: test results from a laboratory that is no longer in existence and whose practices and methods were seriously flawed. In *Daubert's* terms, Unigenetics' rate of error was unacceptable. Doctor Rima's response to one of my questions provided a cogent reason for so concluding. He noted that Unigenetics was the only laboratory commercially testing CSF or blood for the presence of measles virus. Snyder Tr. at 927A. He then commented:

> Let me explain this. I mean, if the technology had been validated, then Dr. O'Leary would have found me and Oldstone and several other people interested in measles virus at his door saying, can you help us resolve issues about not only this disease. I can give you other diseases where there is a question about the formation of measles virus in - - disease, in otoclerosis. And I'm involved in several of these instances where people are struggling to find a link or an etiology for a disease which has no known etiology. And so, if indeed that technology had been validated, if that indeed had been the circumstance, a lot of people would have knocked on O'Leary's lab and said you can do something which we can't do. And there would have been a flood of people coming to him independent of the litigation of some. But that flood hasn't taken place for the very simple reason that everyone who has looked at it said, no, actually, this technology does not work. What he claims he can do he cannot do. What he claims, he simply has not been able to give us the sort of confidence in his technology that would allow us to start looking at it from a research perspective. That's a research perspective. That is a very different perspective even from the perspective of a diagnostic lab that is going to test children for pathological conditions that there are. So I would have said I would have been the first at his door...But it was clear that the company that was set up by Unigenetics had only one trading activity and that was to test measles presence in samples from the litigants in the U.K...We came quickly to the conclusion that some of the practices that I described here, some of the sloppiness, some of the inconsistencies in the data were there and they led us to the conclusion that this simply does not work.

Snyder Tr. at 927A-29.

2. Logical Sequence of Cause and Effect.

Under *Althen*, the logical sequence of cause and effect must be supported by a "reputable medical or scientific explanation, *i.e.*, by evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant*, 956 F.2d at 1148. In *Capizzano,* the court confirmed that circumstantial evidence and medical opinion, including those of treating physicians, may be sufficient under some circumstances to satisfy *Althen's* second prong. 440 F.3d at 1326 (noting that "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect shows that the vaccination was the reason for the injury.'"). *Id.*

Special masters examine the soundness and reliability of the offered medical or scientific explanations. *See Althen*, 418 F.3d at 1278 (stating that a logical sequence is supported by a "reputable" medical or scientific explanation); *see also* Vaccine Rule 8(c) (instructing special masters to ensure evidence is "relevant and reliable").

Petitioners' experts and fact witnesses attempted to establish the logical connection between Colten's vaccinations and his medical condition. The primary and direct evidence of a connection was Unigenetics' test results. For reasons explained at length, *supra*, I find insufficient indicia of reliability in Unigenetics' testing program in general, and in Colten's results in particular, to show the presence of measles virus in his brain. The lack of a logical connection in the CSF results is amply demonstrated by the amount of measles virus RNA purportedly found, an amount too great to be biologically plausible.

Absent evidence of persisting measles virus, Dr. Kinsbourne was unwilling to opine in favor of vaccine causation in Colten's case. This tells me that Dr. Kinsbourne reasoned backwards. From the presence of measles virus, he developed a theory about how the virus could cause brain inflammation and damage the excitation-inhibition balance in brain chemistry, resulting in autism's symptoms. Unfortunately, his theories are not logical, based on everything known about measles virus. When measles virus persists, it kills within months or years.

Doctor Bradstreet's opinions on causation informed his treatment of Colten, and for that reason, if for no other, they warrant consideration. It is clear that Colten's condition materially improved between the time he began speech therapy in April, 1999, and the time of the hearing. However, it is far from clear that Colten's improvement was due to Dr. Bradstreet's treatment. It is even less clear that the treatments were designed to remove a dangerous virus from his body, and the evidence that any of the treatments were capable of doing so is nonexistent.

Colten's parents clearly believed in Dr. Bradstreet's treatment regimen. They saw evidence of behavioral responses to IVIG and secretin therapy, and reported their observations to health care providers, including those other than Dr. Bradstreet. Their subjective beliefs also warrant careful consideration. However, the objective evidence

regarding Dr. Bradstreet's therapies is not particularly persuasive. Colten got worse when chelated. Secretin may have helped with bowel symptoms, and even with behavior, but, objectively, secretin has been shown to be ineffective in autism treatment. As Dr. Wiznitzer noted, Colten had digestive and allergy problems that may have been helped by dietary restrictions. Colten's parents clearly believed that IVIG therapy helped Colten. Although my detailed review of Colten's medical records, and a comparison of those records against objective measures of his performance in school and speech therapy makes me, like Dr. Skoda-Smith, less sanguine about IVIG's effectiveness, even accepting their assessment does not advance Colten's claim for causation. IVIG therapy has not been shown to be effective against measles virus. It has not been shown to be effective in treating anti-MBP antibodies, a problem that had disappeared by the time the treatment was initiated, and which did not appear to resurface during those periods when IVIG therapy was suspended. The many dietary supplements may or may not have helped Colten, but, again, there were no reasons advanced to connect them to countering persistent measles virus.

I am unconvinced that Dr. Bradstreet's treatments span the gap between the theory of measles virus persistence and Colten's PDD-NOS. Doctor Kinsbourne's conclusions regarding causation in Colten are ultimately based on the presence of a persistent measles virus in his brain. Snyder Tr. at 452A-52B. However, the absence of any credible evidence that Colten actually had measles virus in his brain eliminated the connector between Dr. Kinsbourne's theory and Colten's condition.

3. A Proximate Temporal Relationship.

The best that can be said about this aspect of petitioners' case is that the probable onset of Colten's regression in language occurred after his vaccination, although the videos demonstrated some early, subtle indicators of communication and socialization difficulties months prior to the vaccination. Onset after vaccination is not enough, standing alone, to satisfy *Althen's* third prong. 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.

Doctor Kinsbourne opined that the symptoms must have manifested after vaccination for him to opine that the vaccine caused the condition. Snyder Tr. 536A-37A. Because his opinion was so clearly based on the manifestation of autistic regression as an indication that "something" was happening in the brain at that time, it appears that the temporal relationship between vaccination and manifestation of regression had to be reasonably close. He did not place an absolute outer limit of how soon after the vaccination the symptoms had to manifest. He could not opine on how long after vaccination the virus might enter the brain. Cedillo Tr. at 530-32A. Thus, it appears he did not know what a biologically appropriate temporal relationship would be, although his testimony in *Cedillo* suggested that, after with onset greater than three months post-vaccination, he would be less willing to opine that the MMR vaccine

caused ASD. Cedillo Tr. at 1177-78A.

Both Drs. Kinsbourne and Bradstreet opined that the onset of Colten's PDD-NOS was in early May, 1998. For the reasons noted above, I do not accept the factual premises upon which these opinions are based because they conflict with contemporaneously created, and reasonably detailed, medical records. There was no clear demarcation point established for Colten's loss of skills. To the extent that petitioners rely on Colten's May and June, 1998 illnesses for onset and connection to his vaccination, the pharyngitis, fever, and weight loss all manifested prior to his MMR vaccination.

I find that his speech problems began at some point between when he was 17 and 19 months of age, at a time when his immune system was functioning normally, and there was no evidence that he had a delayed reaction to his measles vaccine. The immune system testing done when he was 16 months old (during his hospitalization) and by Dr. Otegbeye several weeks later demonstrated that Colten's immune system was functioning appropriately after his vaccination. His IgG levels were entirely normal. Doctor Kinsbourne relied in some measure on a malfunctioning immune system to explain why Colten allegedly failed to clear the virus. The objective evidence is that at the time Drs. Kinsbourne and Bradstreet claimed his symptoms manifested, Colten's immune system was functioning appropriately.

In her first report to a health care provider of behaviors consistent with ASD, Mrs. Snyder placed onset when Colten was 19 months of age. Dating it to when Dr. Otegbeye recorded a vocabulary suggestive of language delay (although he did not note it as such) would place onset of word loss at 17 months of age. This time frame fits squarely within the period when most parents notice loss of skills or developmental plateaus, according to the testimony of respondent's experts. It is also consistent with the evidence that strongly genetic disorders can manifest at pre-programmed time frames, long after birth, without any outside triggering events.

Doctor Kinsbourne may have relied upon the appearance of symptoms of MIBE (months after vaccination) and SSPE (years after vaccination) for the lack of any firm outer limit. If he were reasoning by analogy to these conditions, it would not matter when the symptoms manifested. This is yet another example of Dr. Kinsbourne "cherry-picking" data that supports his hypothesis, but blithely ignoring facts that contradict it. If he relied upon the slow action of measles virus in SSPE for the outer limit of a temporal relationship, he was ignoring the damage to neurons and the progressively debilitating mental status that occurs when measles virus invades the brain and persists there.

If Dr. Kinsbourne adopts the three-month outer limit he alluded to in *Cedillo*, it is possible that Colten's loss of skills manifested within that time frame. However, to the extent Dr. Kinsbourne relies on Colten's symptoms in May, 1998, to establish a proximate temporal relationship to his vaccination, the factual predicate upon which his

opinion rests is absent.

4. No Burden on Respondent to Establish an Alternate Cause.

Petitioners have failed to establish any of *Althen's* three factors. Thus, they have failed to establish that Colten's vaccines were a substantial cause of his injury. Because they have failed to establish causation by a preponderance of the evidence, the burden never shifted to respondent to establish an alternative cause for Colten's condition. *De Bazan*, 539 F.3d at 1353-54.

5. Summary.

To conclude that Colten's condition was the result of his MMR vaccine, an objective observer would have to emulate Lewis Carroll's White Queen and be able to believe six impossible (or, at least, highly improbable) things before breakfast. The families of children with ASD and the court have waited in vain for adequate evidence to support the autism-MMR hypothesis. Although I have the deepest sympathy for families like Colten's, struggling emotionally and financially to find answers about ASD's causes, and reliable therapies to treat ASD's symptoms, I must decide Colten's case based on the evidence before me. That evidence does not establish an adequate factual basis from which to conclude that Colten's condition was caused by his vaccines.

Section IX. Conclusion.

Petitioners have not demonstrated by a preponderance of the evidence that Colten's condition was either caused or significantly aggravated by his vaccinations Thus, they have failed to establish entitlement to compensation and the petition for compensation is therefore DENIED. In the absence of a motion for review filed pursuant to RCFC, Appendix B, the clerk is directed to enter judgment accordingly. [537]

IT IS SO ORDERED.

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

[537] 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.

APPENDIX A

Acrodynia: Also known as “Pink disease,” a disorder caused by ingestion of mercurous chloride in the form of teething powder.

ADI-R: Autism Diagnostic Interview-Revised. A checklist used in autism diagnosis.

ADOS-G: Autism Diagnostic Observational Schedule-Generic. A checklist used in autism diagnosis.

Affinity maturation: The process by which, over time, the B cells with the highest affinity for a particular pathogen are selected for continued reproduction. This is the method by which life-long immunity to a particular pathogen can be conferred after natural exposure or immunization.

APCs: Antigen Presenting Cells.

Apoptosis: programmed cell death.

ASD: Autism Spectrum Disorder. A term synonymous with PDD, used to describe a number of neurodevelopmental disorders.

Autism Gen. Order 1: The general order from the Office of Special Masters that created the Omnibus Autism Proceeding.

B cells: Adaptive immune system cells that form part of its humoral arm. Naive B cells have not yet encountered the antigens they are capable of recognizing. Activated B cells produce antibodies (serum proteins), generally called immunoglobulins.

CARS: Childhood Autism Rating Scale. A method for diagnosing autism.

Case-control study: A case-control study compares a group with a disease or condition to a control group without the condition. The term “retrospective” is applied to such studies because they begin after onset of the condition being studied and look backwards toward possible causal factors.

CBC: complete blood count.

CD4+ T cells: T lymphocytes that are part of the humoral arm of the adaptive immune system.

CD8+ T cells: T lymphocytes that are part of the cell mediated arm of the adaptive immune system, sometimes called cytotoxic T cells.

CDC: Centers for Disease Control and Prevention.

Cell mediated arm: One arm of the adaptive immune sytem. It consists of CD8 T cells, and is focused on killing intracellular pathogens.

Chelation: The use of chemicals to break the bond formed between some heavy metals and body tissue, which allows the heavy metals to bind to the chelating agent and then be excreted.

Class switching: The changing of a B cell's production of antibody type, from IgM to either IgG, IgA, or IgE antibodies.

Cohort study: A type of epidemiologic study sometimes called an incidence study. It compares the new onset of a disease in two groups of individuals, with one group exposed to something and the other group unexposed. By following the two groups over a period of time, and measuring the incidence of the disease in the exposed and unexposed groups, it is possible to determine if the exposure played a role in the development of the disease. If the incidence of the disease is the same in both groups, the exposure is unlikely to have had an effect on the development of the disease.

Concordance rate. The percent of the time that two individuals or groups of individuals share the same condition. A 100% concordance rate for identical twins indicates that a condition is entirely genetic; a figure less than 100% indicates that factors other than genetics play a role in the development of a disease or disorder.

Colitis: Colitis is inflammation of the colon (the large intestine). In ulcerative colitis, inflammation is generally limited to the lining of the colon, without deep penetration into the muscular layer of the bowel. The inflammation begins at the anus and extends back into the colon in a contiguous pattern. It may involve only a portion of the rectum or extend to the entire colon.

Crohn's disease: Crohn's disease is a chronic inflammatory disease that may occur in any part of the gastrointestinal tract from the mouth to the anus, but, most commonly, it involves the terminal ileum. It may involve the lining of the bowel, but may also penetrate the wall of the bowel itself.

CT: Threshold cycle. The cycle of PCR amplification at which fluorescence is detected, indicating the presence of the target substance in the unknown sample.

Cytokines: Cytokines are hormone-like proteins that communicate between immune system cells. In essence, they are messages or orders sent from one cell to another.

Cytotoxic T cells: Sometimes called killer T cells. These mature T cells attack cells infected with viruses. Killer T cells are also called CD8 T cells, after the type of receptor found on their surface.

DC: Dendritic cells. They are the most important of the antigen presenting cells. Before activation, they act like phagocytes to engulf invading pathogens. After activation, they present antigens from the invaders to B and T cells in the lymph nodes.

DMSA: A chelating agent.

DNA: Deoxyribonucleic acid.

DSM: Diagnostic and Statistical Manual. The U.S. manual containing standard diagnostic criteria for mental diseases and disorders. It contains a numeric code for each recognized condition.

DSM-IV-TR: The current version of the Diagnostic and Statistical Manual (4^{th} Ed., Text Revised).

Dysmorphic: Malformed, resulting from a congenital anomaly.

Ecological study: A type of epidemiologic study that looks at rates of a particular disease over time and compares those rates to exposure levels over the same period. An example of an ecological study would be comparing unemployment rates and suicide rates. If suicide rates go up as unemployment rates also rise, that might indicate there is a relationship between the two events. The inferences that can be drawn from an ecological study is weaker than those from a cohort or case-control study because an ecological study relies on aggregated rather than individual data.

EEG: Electroencephalogram.

Enterocolitis: Colitis (inflammation) of both the small and large intestine.

EPA: Environmental Protection Agency.

GABA: Gamma aminobutyric acid. It is the primary inhibitory neurotransmitter in the brain.

Gammaglobulins: Antibodies produced by B lymphocytes of the IgG class. These are the antibodies that confer long-term immunity after exposure to and defeat of a specific pathogen.

GFCF: The gluten-free and casein-free diet, which involves removing all foods

containing gluten (primarily wheat products) and casein (primarily milk products) from the diet.

Humoral arm: One part of the adaptive immune system. It consists of B cells and CD4 T cells.

IBD: Inflammatory bowel disease. This term encompasses several disorders of the digestive tract, including ulcerative colitis, indeterminate colitis, nonspecific colitis, microscopic colitis, and Crohn's disease. Its hallmark is the presence of inflammation.

IBS: Irritable bowel syndrome. Bowel symptoms consisting of constipation or diarrhea, or a alternating of the two symptoms.

ICD-10: International Classification of Disease Manual. The disease classification system used in Europe.

IFN-α: Interferon alpha. A cytokine given off by cells being attacked by viruses. It activates NK cells.

IFN-β: Interferon beta. A cytokine given off by cells being attacked by viruses. It activates NK cells

IFN-Y: Interferon gamma. A cytokine that activates macrophages. It is produced by helper T cells and NK cells.

IgA: Antibodies that protect the body's mucosal surfaces.

IgE: Antibodies produced in allergic reactions.

IgG: Also called gamma globulins. These antibodies exist in four numbered subclasses, each with different functions in fighting invading pathogens. IgG antibodies remain in circulation after a pathogen has been defeated, and can mount a rapid response in the case of future encounters, thus providing immunity against subsequent infections.

IgM: Immunoglobulin M. The initial immunoglobulin (antibody) produced by B cells to fight pathogens.

ILNH: Ileal lymphonodular hyperplasia. ILNH is an enlargement of the lymph nodes in the small intestine and colon.

Ileum: The lower portion of the small intestine. The terminal ileum is the last portion of the small intestine where it joins the colon.

Inorganic mercury: Any form of mercury, including elemental mercury, that does not contain a carbon compound.

Koplik spots: Small white spots appearing inside the mouth and on the tongue. They are pathognomonic of wild-type measles infections. Nothing else causes them.

LKS: Landau-Kleffner Syndrome. Children with this syndrome experience an acquired language disorder, most probably as a result of a form of epilepsy. This language disorder has similarities to ASD, including abnormal development of spoken language, impaired ability to initiate or sustain conversation, and stereotyped, repetitive, and idiosyncratic language. Differences between the two syndromes include an earlier loss of language in ASD, more dramatic loss in LKS, and a different behavioral profile in ASD (core symptoms of ASD). EEG findings in LKS are striking. The etiology of LKS is unknown.

LNH: Lymphonodular hyperplasia. It is characterized by small nodules present below the mucosal level in the colon, formed by the B lymphocytes coalescing to form a nodule. Lymphoid nodules are part of the immune system of the bowel. When the B lymphocytes are stimulated by foreign tissue, the B cells reproduce and the underlying lymphoid nodule grows larger.

LPS: Lipopolysaccharides. They are molecules contained in the cell walls of many bacteria. LPS can activate macrophages.

Lymphoid nodules: Small nodules present below the mucosal level in the colon, formed by B lymphocytes coalescing to form a nodule. Lymphoid nodules are part of the immune system of the bowel.

Lymphopenia: A decrease in the number of circulating lymphocytes.

Macrophages: A type of specialized white blood cell that engulfs invading pathogens and produces cytokines. Activated macrophages can function as antigen presenting cells.

MBP: Myelin basic protein. Myelin, the insulation that sheathes the brain's axons and spinal nerves, can be damaged in a number of ways. When damaged, internal components of the myelin, which include myelin basic protein, leak out into the surrounding tissues, and the body may produce antibodies against this protein.

Mcg: Microgram, usually abbreviated as "µg." It is one-millionth of a gram.

Methylmercury: A type of organic mercury found primarily in seafood, including fish and whales.

MIBE: Measles inclusion body encephalitis. A disease caused by persistent measles virus in individuals who were immunocompromised at the time of the measles infection or vaccination.

Mg: Milligram, usually abbreviated “mg.” One one-thousandth of a gram.

MMR: Measles, Mumps, and Rubella vaccine, consisting of live, attenuated viruses.

Neutrophils: A type of white blood cell that kills bacteria and viruses and can bind to IgG1 antibodies to activate them.

NK: Natural killer cells. A part of the innate immune system capable of killing bacteria, virus infected cells, tumor cells, and other pathogens. They produce cytokines, primarily IFN-γ. They are activated by IFN-α and IFN-β.

OAP: Omnibus Autism Program.

Organic mercury: Any form of mercury containing carbon atoms. Ethyl- and methylmercury are both types of organic mercury.

OSM: Office of Special Masters.

Opsonization: The method by which antibodies bind to the surface of invading pathogens to signal immune system cells to attack the invaders.

PBMC: Peripheral Blood Mononuclear Cells. PBMCs are the lymphocytes, macrophages, and dendritic cells that remain in blood after the removal of red blood cells, platelets, and neutrophils from peripheral blood. Measles virus (wild-type and vaccine strain) can infect all types of the PBMCs *in vitro*, and presumably *in vivo* as well.

PCR: Polymerase Chain Reaction. A method of amplifying DNA exponentially.

PDD: Pervasive Developmental Disorder. The DSM-IV-TR term used to describe a number of neurodevelopmental disorders. Synonymous with “ASD.”

PDD-NOS: Pervasive Developmental Disorder-Not Otherwise Specified. A “catch-all” category of the DSM-IV-TR that encompasses individuals with neurodevelopmental disorders that meet some, but not all, of the diagnostic criteria for Autistic Disorder.

Phagocytes: Cells, including macrophages and neutrophils, that engulf or ingest microorganisms or particles in a process called “phagocytosis.”

PIEM: Post-measles viral encephalomyelitis, often called post-measles viral encephalitis.

Prevalence study: A type of ecological study, sometimes called a cross-sectional study. Prevalence studies look at a population at a single point in time, and assess all of the individuals in the sample for disease and the characteristics suspected to be associated with the disease.

PSC: Petitioners' Steering Committee. A group formed from the attorneys representing petitioners in the Omnibus Autism Proceeding to represent the interests of autism petitioners and to develop the general n case for vaccine causation of ASD.

RfD: Reference dose. The daily dose of a substance, as averaged over a lifetime, that would not be expected to have an adverse effect.

RNA: Ribonucleic acid.

RT: Reverse transcription. A method of converting RNA to DNA. Note that some confusion may arise because the abbreviation "RT" was sometimes used in evidence to refer to "real time" PCR amplification. Occasionally documents or witnesses may have referred to RT-RT-PCR, meaning real time, reverse transcription PCR.

SCID: Severe Combined Immunodeficiency Disease. A type of primary (genetic) immunodeficiency.

SOP: Standard Operating Procedure. A set of guidelines and standards for conducting PCR testing in a particular laboratory.

SSPE: Subacute sclerosing panencephalitis. A devastating and ultimately fatal disease caused by persistent measles virus.

T cells: Lymphocytes that mature in the thymus. There are several classes of T cells. Naive T cells have both CD4 and CD8 receptors on their surface. When triggered by other cells or cytokines, they mature and select one type of receptor. Cytotoxic (or killer T cells) have CD8 receptors and kill virus-infected cells. T helper cells (Th) cells have CD4 receptors on their surface and trigger other immune system cells to fight invaders. T regulatory cells help calm down immune system reaction after a pathogen has been defeated.

TCVs: Thimerosal containing vaccines. In the past, these included most childhood vaccines. Currently, only the influenza vaccine contains more than trace amounts of thimerosal.

Th cells: T helper cells. These T cells trigger reactions in other immune system cells. They have CD4 receptors. They are activated in the lymph nodes by dendritic cells, which causes them to proliferate. After proliferation, they mature into effector T cells.

Th1: T cells that express a certain type of cytokine, including IL-2, IFN-γ, and TNF, that help the body develop an immune response tailored to the nature of the invading pathogen, particularly viral or bacterial attacks on blood and tissue. It is considered a cell mediated response.

Th2: T cells that express a certain type of cytokine, including IL-4 and IL-5, that help the body develop an immune response tailored to the nature of the invading pathogen, particularly parasitic or mucosal infections. It is considered an antibody response

Theory 1: The theory that a combination of MMR vaccine and TCVs cause ASD.

Theory 2: The theory that TCVs cause ASD.

TLR: Toll-like receptors are structures on the surfaces of immune system cells that allow them to "recognize" proteins produced by invading pathogens, or cytokines that signal the presence of pathogens. Recognition triggers activation of the immune cell.

TNF: Tumor necrosis factor. A cytokine that can kill tumor cells and virus infected cells and that can activate other immune system components.

T Reg cells: T regulatory cells. These T cells damp down Th 1 and Th 2 responses after the immune system has successfully defeated a pathogen.

Ulcerative colitis: An inflammation of the large intestine (colon), with the inflammation generally limited to the lining of the colon, without deep penetration into the muscular layer of the bowel. The inflammation begins at the anus and extends back into the colon in a contiguous pattern. It may involve only a portion of the rectum or extend to the entire colon.

Virion: A complete and infectious virus.

µg: Microgram; one-millionth of a gram, sometimes abbreviated "mcg."

APPENDIX B

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Section I. Omnibus Proceedings .