OFFICE OF SPECIAL MASTERS

September 26, 2003

JOANNE BAKER, legal representative for JONATHAN BAKER,	*	
Petitioner,	*	No. 99-653V PUBLISHED
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Michael J. Katarincic, Milwaukee, WI, for petitioner.
Tami C. Parker, Washington, DC, for respondent.

DECISION

MILLMAN, Special Master

Petitioner filed a petition initially pro se August 5, 1999 under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10 et seq., alleging that her son Jonathan Baker[1] (hereinafter, "Jonathan") suffered an adverse reaction taking the form of insulin dependent diabetes mellitus (IDDM) or Type I diabetes as a consequence of all of his childhood immunizations.

[1] Jonathan's original last name was Berenberg. Petitioner changed her name and his to Baker in 1999. Med. recs. at Ex. 4, p. 11. Petitioner is a dentist. Jonathan's father is an internist. Med. recs. at Ex. 5, p. 1.

Petitioner submitted a VAERS[2] report as her petition. She completed the form herself on July 31, 1999, alleging that Jonathan was vaccinated on July 1, 1996 and diagnosed with diabetes on May 3, 1999. The vaccinations were Dt, polio, HiB, and hepatitis B. She describes the adverse signs and symptoms as rash, fever, swelling leg, and diabetes mellitus. See filing of August 5, 1999.

On February 20 and 21, 2003, the undersigned held a hearing. Testifying for petitioner was Dr. John B. Classen, a general practitioner. Testifying for respondent were Dr. Neal Halsey, an epidemiologist, Dr. Burton Zeiman, an immunologist, and Dr. Barry Bercu, a pediatric endocrinologist.

FACTS

Jonathan was born on January 3, 1996 by Caesarean section because of failure to progress and fetal distress. His mother was almost 38 years old. Med. recs. at Ex. 1; Ex. 3, pp. 4, 37, 39. He received DPT, OPV, hepatitis B, and HiB vaccinations on March 3, 1996, May 1, 1996, and July 11, 1996, when he was 2, 4, and 6 months of age. He received MMR and varicella vaccines on February 5, 1997. He received HiB and DPT on May 15, 1997. Med. recs. at Ex. 4, p. 2, and Ex. 5, p. 1.

On October 9, 1997, when Jonathan was 19 months old, his pediatrician wrote that he still was not talking. Med. recs. at Ex. 5, p. 4.

On August 5, 1998, Jonathan saw Dr. John T. Wells, a pediatric neurologist. His history included fetal bradycardia. Jonathan had been in foster care for three months because of a custody dispute. He had limited expressive language, and was shy. He had a normal motor examination. Med. recs. at Ex. 6, pp. 7, 8.

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[2] Vaccine Adverse Event Reporting System.

On May 4, 1999, Jonathan saw Dr. Fenella Greig, a pediatric endocrinologist, at the Mt. Sinai Diabetes Center. He was diagnosed with IDDM on May 3, 1999. His father had taken him to the emergency room on May 3, 1999 for evaluation of a few days' history of polydipsia (chronic excessive thirst), and polyuria (excessive urination) without vomiting or lethargy. There was no family history of IDDM. Jonathan was diagnosed with Type 1 diabetes mellitus with hyperglycemia, with ketonuria, but without acidosis. Med. recs at Ex. 7, pp. 51, 53.

TESTIMONY

Dr. John Barthelow Classen testified for petitioner. Jonathan Baker was diagnosed with IDDM on May 2, 1999 when he was three years and four months old. There was a hiatus of 38 months after his initial childhood immunizations and 27 months after his MMR and varicella immunizations on February 5, 1997. Dr. Classen majored in zoology in college. He received a masters in business administration after obtaining his MD because medical research was his interest. He has never been board-certified in anything. He earns a living in a walk-in clinic. He has patents for vaccine safety which describe methods of testing vaccines and hopes that pharmaceutical companies will pay his corporation (of which he is the sole employee) licensing fees for these as well as for vaccine schedules he has patented.

Dr. Classen's opinion is that, in children under the age of 7 years, vaccinations cause 50%[3] of IDDM, depending on what vaccines are given. Tr. at 13-14.. He derived the 50% figure from analyzing Finnish data on Hemophilus B influenza (HiB) vaccine, which he stated caused 25% of IDDM. He added the relative risk from other vaccines to arrive at the 50% figure. Tr. at 14.

[3] Occasionally, Dr. Classen testified the figure was 51%, not 50%. He never clarified why or how he increased the percentage.

His opinion is that Jonathan's childhood vaccinations caused his IDDM. He thinks he is qualified as an epidemiologist. He trained at the National Institutes of Health under an immunologist. His opinion is that in the first six weeks of life, immune stimulation protects against autoimmune diseases. Vaccines are immune enhancers. Dr. Classen claims expertise in autoimmunity, its onset and trigger. Tr. at 35. He also holds himself out as an expert in epidemiology. Tr. at 30, 35. As a clinician, he said he is an expert in treating certain diseases, such as sewing up lacerations. Tr. at 37.

Dr. Classen testified that after doing research, he discovered the downside of vaccines. He spends 20 hours a week in vaccine research and pharmaceutical work, and 20 hours a week in the clinic. He co-authored letters and articles with his first cousin, Dr. David Carey Classen, an infectious disease specialist and pharmacoepidemiologist. Dr. David Classen lists only one co-authored article with Dr. John Classen in his CV, whereas Dr. John Classen lists eight articles or letters co-authored with Dr. David Classen. To explain why his cousin listed only one co-authored article on his CV, Dr. John Classen said that Dr. David Classen had done research for pharmaceutical companies but they do not like Dr. John Classen's work.

Dr. Classen admitted he has no formal training in immunology or virology. His only training in epidemiology was in medical school. He obtained a general medicine certificate from general medicine at the Greater Baltimore Medical Center so that he could work in walk-in clinics to earn his living.

His only training in pediatrics was in medical school. He listed his patent applications in his CV. His CV consists of letters to the editor, patents, and abstracts, with papers, some of which are drafts.[4]

Dr. Classen testified that there are other causes for diabetes besides vaccines. However, except for congenital rubella syndrome, there is a limited ability to detect these other causes of diabetes. Tr. at 21. For a natural infection, it is difficult to know when the onset is. Tr. at 22.

His understanding of a mechanism for how vaccines cause IDDM is hypothetical. Tr. at 67. In very young children, over two months of age, vaccination may trigger a process where the macrophages damage islet cells in the pancreas. In older individuals, some autoimmune process is probably ongoing and the incubation period can be shorter because the person is already substantially damaged. Tr. at 71. The size of the individual matters. A small person does not need so many islet cells. Tr. at 23. In young persons, there would be a three-year interval to clinical disease. In older persons, there would be a five-year interval.[5] Tr. at 72. The factors involved in IDDM are genetic, and preexisting, as well as based on the individual's size. Everyone is not born with the same number of islet cells.

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[4] Dr. Classen denies that he is egotistical, although he did liken himself to Darwin in an interview, but he admits that he does not have Darwin's status. Tr. at 25. Similarly, although he likened himself to Aristotle in the same interview, he meant a scientist such as Copernicus or Galileo who opined that the earth went around the sun, a point of view unacceptable in the times in which these scientists lived. Tr. at 25, 55. Thus does Dr. Classen depict his own unpopularity in the medical and scientific world. Dr. Classen testified that "many people say that science runs by consensus or something like that, and that's not true." Tr. at 26.

[5] This contradicts his prior statement that older persons may have a shorter interval to clinical disease because of prior damage but Dr. Classen explained that genetics can affect it.

Dr. Classen said that when vaccinations were stopped, the incidence of IDDM went down in England and Denmark. In Finland, the incidence was constant when the immunization schedule was not changed. Tr. at 81. Dr. Classen stated that experimental evidence showed that HiB causes IDDM. Generally, he said that odds ratio and relative risk would be similar although calculated differently. He also stated that the onset of IDDM is clustered. The natural history of IDDM is 3.2 years, and a 3.25-year interval is coherent with that natural history. Tr. at 102. Congenital rubella syndrome also causes IDDM, but the clinical onset occurs at age 16. Tr. at 103, 166.

Dr. Classen explained his opinion of causation as being based on meeting eight of nine criteria of proof by Sir Austin Bradford-Hill. Tr. at 96-97, 109. These are: strength of association, consistency of findings, temporality, coherence, plausibility of association (mechanism of action), analogy, biological gradient, animal experimentation, and clustering.

Dr. Tuomilehto, a Finnish epidemiologist, found 3.2 years was the median onset of diabetes in a very elegant study. Tr. at 105. In a prospective, randomized study of 120,000 Finnish children, the ones who received HiB vaccine at three months had an extra cluster of IDDM. Tr. at 107. HiB is analogous to other vaccines. Tr. at 110.

Dr. Classen reviewed HiB in Finland on Medline. Tr. at 113. It was the largest clinical trial of vaccine efficacy. Id. It was randomized over a two-year period from October 1, 1985 through August 31, 1987 by whether the child was born on an even or an odd day. Tr. at 116. In one group, four doses of HiB were given, starting at three months of age. In a second group, one dose of HiB was given at two years of age. Tr. at 113. The FDA, the CDC, and the Finnish Public Health Service approved the study. Tr. at 113-14. Dr. Tuomilehto is in charge of the Diabetes Register database for children under age 15. In 1996, Dr. Classen wrote Dr. Tuomilehto about following the

Finnish development of IDDM in children at ages 2, 5, and 7. Tr. at 116..

Dr. Classen stated that the Finns omitted data that would have showed clustering of IDDM cases (Ex. 67) and compared only the one-dose vaccinated group (but not the four-dose vaccinated group) with the historical unvaccinated group born two years before HiB was administered in Finland.[6] Tr. at 134, 159. Dr. Classen's article (Ex. 23) includes data showing clustering. He compared the four-dose group at seven years with the historical unvaccinated group and found statistical significance in the number of cases of diabetes. The Finns, however, analyzed data at 10 years, not 7 years, and compared the four-dose group only with the one-dose group. Tr. at 121.

Dr. Classen testified that, at seven years, one should see a difference. Between 7 and 10 years of age, other causes of IDDM occur, the signal decreases, and there is no difference. Tr. at 121, 123. Most of the signal occurred before seven years of age. The cluster of IDDM occurred 36 months (three years, three months) after vaccination when comparing one dose versus four doses. Tr. at 135-36. Dr. Tuomilehto never mentioned clustering in his paper. Tr. at 155. In other papers, he has mentioned only space-time clustering. Tr. at 141. Dr. Classen states that Dr. Tuomilehto reached his conclusion by ignoring some of his data, i.e., the clustering. Tr. at 138. Dr. Tuomilehto did not compare the four-dose group with the no-dose group. Dr. Tuomilehto's relative risk is too

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[6] Although Dr. Tuomilehto did compare the one-dose group (immunized at two years of age and born on even days from 1985 to 1987) with the historical controls (born from 1983 to 1985) who were unimmunized, he stated that the historical controls were "less than ideal as many other and often unknown factors may influence secular trends between birth cohorts." "Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study," by M. Karvonen, Z. Cepaitis, and J. Tuomilehto, 318 *BMJ* 1169, 1171 and Table 2 (May 1, 1999). P. Ex. 67.

low and he did not use a seven-year endpoint. Zero to seven is statistically significant. Zero to five, zero to two, and five to ten are not statistically significant. Tr. at 131-32.

Dr. Classen quoted Dr. Tuomilehto as saying that there is a two- to four-year lag time between the potential trigger and onset of IDDM. Tr. at 164. Twelve years prior to HiB vaccination in Finland, the incidence of IDDM was constant at a rate of 39 per 100,000. Tr. at 176. The same incidence occurs in the control population, but not in the vaccinated population, where it is 46 per 100,000 among five- to nine-year olds. Id. He posits an extra 58 cases of diabetes per 100,000 among vaccinees. Tr. at 179. Those who received four doses had a higher incidence of IDDM than those who received one dose, which had a higher rate than those who were unimmunized. Tr. at 184. This is consistent with biological gradient. Id.

Non-obese diabetic (NOD) mice who received DPT, HiB, and IPV (polio) vaccines had a higher incidence of IDDM than NOD mice who did not receive them. Tr. at 184-86.

Dr. Classen cited Dr. Neal Halsey's paper on hepatitis B vaccine and demyelination as support for Dr. Classen's assertion that small studies support a conclusion of causality even if the association they show is not statistically significant. Tr. at 192-93. Small studies, if well-controlled and -designed, add significant insight, according to Dr. Classen. Tr. at 195, 196-97. The CDC concluded that there was not a statistically significant risk of diabetes after HiB vaccination. Tr. at 198.

After some of his vaccinations April 2, 1996, Jonathan had a very sore, swollen, red leg with a total body rash and fever. This showed prominent activation of his macrophages. This is a localized inflammatory response rather than an immune response. Tr. at 210. The pancreatic islet

cells make an agent that attracts macrophages. HiB vaccine increased the macrophages. B and T cells initiate an autoimmune response after the macrophages get into the pancreas. Tr. at 212, 214.

This is analogous to what happens with other vaccines. Tr. at 215. After discontinuing DPT and BCG vaccines in the United Kingdom and Denmark, the incidence of IDDM decreased.[7] Tr. at 216, 242. In Finland, after MMR was instituted, the incidence of IDDM rose two to four years after vaccination from 23 to 33 cases. Tr. at 219-20. Over a five-year period, when the Finns changed their pertussis vaccine by adding a second strain, the incidence of IDDM increased. Tr. at 234. Cumulative vaccines multiply the risks. Tr. at 227. Dr. Classen got a relative risk of two and an odds ratio of two by multiplying one relative risk by another relative risk. Tr. at 247-48. The randomization in the Finnish study eliminates other risk factors besides HIB vaccine by dividing the groups into those born on even and odd days. Tr. at 266-67.

The Institute of Medicine (IOM), NIH, and the Institute of Vaccine Safety reject Dr. Classen's theory that vaccines cause diabetes. Tr. at 261-62, 330-31, 368. There are no articles in the literature by other authors saying what he and David Classen say (that vaccines cause IDDM). Tr. at 263. IDDM occurs almost always due to an environmental trigger which is not necessarily vaccination. There is no evidence for his theory that chronic infection causes IDDM. Tr. at 294.

With NOD mice, 80% of female mice develop IDDM compared to 20% of males. Tr. at 295. In humans, more males develop IDDM than females. Tr. at 295-96. In the 80% of NOD female mice, most develop diabetes in the absence of intervention. Tr. at 296.

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[7] When the court questioned Dr. Classen's conclusion that a decrease in vaccination led to a decrease in IDDM because Figure 2 in his Exhibit 55, page 39, showed just the opposite, i.e., that when the incidence of vaccination declined, the rate of IDDM did not, Dr. Classen replied, "I wouldn't expect the Court to agree with every paper that we publish." Tr. at 240, lines 13-21.

In Exhibit 23, the unimmunized group in the Finnish data was not randomized. Tr. at 303. Dr. David Classen designed and funded the paper. Dr. John Classen did the analysis, which David Classen reviewed. Tr. at 306. Dr. Classen thinks the epidemiological community accepts multiplying different odds ratios and relative risks from different vaccines and different studies to arrive at the cumulative effect of vaccines. Tr. at 311. Jonathan had a rash on two occasions (January 31, 1996 and February 5, 1996) before he received any vaccines. Tr. at 314. Dr. Classen has a "certain respect" for his former NIH supervisor, Dr. Shevach, "in certain ways." Tr. at 316.

Dr. Neal A. Halsey testified for respondent. He is board-certified in pediatrics and pediatric infectious diseases. Tr. at 335. He is a professor in the areas of infectious disease and vaccines in the Department of International Health at the School of Public Health and Pediatrics at the Johns Hopkins University School of Medicine, and Director of the Institute of Vaccine Safety. He has written 138 peer-reviewed articles and 34 book chapters. Tr. at 336. He peer reviews articles for 15 medical journals and is editor of various journals. Tr. at 337. He is studying HiB in Guatemala. Tr. at 340. He coordinated clinical trials of a new measles vaccine, stopping the attempt to license it in the United States due to adverse events after inoculation. Tr. at 341. He succeeded in changing US policy on polio vaccination to have inactivated rather than oral polio administered. Id. His third child contracted polio from OPV. Id.

Dr. Halsey has served on seven vaccine data and safety monitoring boards. Tr. at 342. He conducted a workshop in March 1998 on vaccines and IDDM (respondent's Ex. H-1) at which Dr. Classen made a presentation. The panel rejected Dr. Classen's conclusions because his analytic methods were incorrect. Tr. at 347. Dr. Halsey's opinion is that there is no evidence that any vaccines cause IDDM, including Jonathan's. Tr. at 346.

There has been an increased incidence of IDDM throughout the world. Children born earlier will have a lower risk of IDDM since the incidence of IDDM increases over time. Tr. at 353. .

Dr. Halsey stated that Dr. Classen confuses hypothesis with fact. Tr. at 354-55. Dr. Classen commits the "ecological fallacy" by ignoring the variability in the incidence or prevalence of diabetes. Tr. at 352, 354. There is a 12-fold variability in the incidence of IDDM in China even though vaccination rates are uniform. Tr. at 501. In countries further from the equator, there is a higher risk of IDDM. Exposure to ultraviolet light may be protective. Tr. at 509-10.

Dr. Halsey has spoken with Dr. Tuomilehto on two occasions. Tr. at 359-60. Dr. Classen uses incorrect and inappropriate methods. Tr. at 367. If he were an introductory student in Dr. Halsey's program, he would not pass an oral exam with his methodology. Tr. at 364. Dr. Classen's theories and methods are not accepted in the epidemiological community. Tr. at 368. When comparing the four-dose group to the one-dose group, the Finnish epidemiologists found no increased incidence of diabetes. Tr. at 347.

None of the studies demonstrates a statistically significant association or a high level of association between vaccination and IDDM. Tr. at 375. Many studies, such as DeStefano's (Ex. 70), show no association. Id. DeStefano's adjusted odds ratio is 0.81, less than one, which means no effect from the vaccine. Tr. at 385.

One cannot multiple odds ratios or relative risks. It is not done and does not make sense. Tr. at 386. One cannot do a meta-analysis of studies of different vaccines. Tr. at 387. There is good evidence to support a genetic cause for IDDM. Tr. at 389. There is no consistency here because other authors reach the opposite conclusion from Dr. Classen. Tr. at 403. Regarding specificity of association, Dr. Classen argues that any vaccine can cause IDDM, which is non-specific, but

vaccines work in different ways and the host-immune response is very different. Tr. at 404. With the Finnish data, Dr. Classen ignored all the data up to three years. Tr. at 394. His cluster analysis is arbitrary and inappropriate. Tr. at 398. As a member of peer-reviewed editorial boards and as a reviewer, Dr. Halsey would not have accepted Dr. Classen's paper, which is Exhibit 23, for publication. Tr. at 399.

There is no strength of association here. Tr. at 401-02. Regarding the criterion of temporality, Dr. Halsey stated one needs exposure before outcome, but there is no consistency of timing. Tr. at 404. There is no temporal association between vaccination and IDDM. Regarding biological gradient, there is no dose-response effect, that is, no difference between one dose and four doses in children who are randomized. Tr. at 404-05.

Regarding biological plausibility, molecular mimicry does not happen. Tr. at 405. The criterion of coherence is not fulfilled because everything does not fit together with what we know. The results of animal studies are inconsistent. They produce only a hypothesis. Tr. at 393. BCG and DPT administered early protects the animal from diabetes. Tr. at 407. The IOM concluded there was no effect in humans. Tr. at 408. Analogy is the weakest criterion.

Dr. Halsey testified that Dr. Classen misinterprets the findings in the studies. Tr. at 414. Whereas Dr. Halsey can discuss the absence of statistical significance in formulating hypotheses, Dr. Classen uses hypotheses to show causation. Tr. at 417-18. Dr. Halsey concluded there was not a statistically significant association between hepatitis B vaccine and demyelination. Tr. at 416.

Dr. Classen overemphasizes the role of vaccines in stimulating macrophages. All infections stimulate macrophages. Tr. at 388, 408. Dr. Halsey is unimpressed with Dr. Classen's testimony that polysaccharide and aluminum in vaccines stimulate macrophages because mere infections

activate macrophages. If activation of macrophages were sufficient to cause diabetes, we would all have diabetes by the ages of 4 or 5 years. Id. Any damaged tissue stimulates cytokines which attract macrophages. Dr. Halsey does not believe that activation of macrophages through vaccines causes the onset of IDDM. Tr. at 421, 423.

The Conference of March 20, 1998 at the Institute of Vaccine Safety reviewed pathology, endocrinology, and epidemiology, not just Dr. Classen's data. Dr. Classen took his father, a retired surgeon, with him to the conference on advice of his brother, who is a lawyer. Tr. at 426, 427. The conference panel members excluded anyone with a direct conflict of interest, including vaccine manufacturers and Dr. Classen because he has patents on the use of vaccines. Tr. at 431.

Dr. Burton Zweiman testified next for respondent. He is professor of medicine at the University of Pennsylvania School of Medicine, who does research on experimental autoimmune disease. He is board-certified in internal medicine and in allergy and immunology. Tr. at 442. He has done experiments on the effects of certain immunizations on cellular immunity. Id. His opinion is that vaccines do not cause IDDM based on the epidemiological evidence, experimental animal studies, and immunology. Tr. at 443. No respected immunologist accepts Dr. Classen's proposed mechanisms of causation. Tr. at 444.

The role of macrophages is to wall off areas of inflammation. Id. Their major function is to digest dead or dying cells. Tr. at 445. When certain types of antibodies are present, one gets an inflammatory reaction. A modest and transient elevation of macrophages occurs long before there is islet cell damage in IDDM. Transient macrophage activation is unlikely to cause direct damage to pancreatic islet cells. Id. Immunological pathogenesis of IDDM involves very slow, progressive

damage to islet cells over a period of years. Tr. at 446. Transient macrophage activation will not persistently damage islet cells. Id.

Dr. Classen's first flaw is that there is no evidence that T lymphocytes perpetuate the damage. Tr. at 447. His second flaw is denigrating the effect of systemic infections which activate more macrophages than vaccinations. Tr. at 447-48. The causative mechanism for IDDM is still not known.

Dr. Classen's third flaw is opining that multiple vaccinations give much more potent stimulation than infections. This is not true. Tr. at 448. There are more multiple surface antigens in infections than there are in aluminum or polysaccharides in vaccines. Tr. at 449. A febrile reaction may be due to the release of cytokines, not interferon alpha, as Dr. Classen testified. Id. A small percentage of people with hepatitis C who were treated with great doses of interferon alpha got autoimmunity. By contrast, after vaccination, cells have to be stimulated in vitro with lipopolysaccharide in order to show secretion of interferon alpha. Tr. at 450..

Dr. Classen's data have major problems. He used the wrong statistical method (Wilcoxon), which is designed for paired data. Tr. at 451. Dr. Classen used two different groups of mice (unpaired data), and did not study response before and after in the same mouse (paired data). He should have used Mann-Whitney for unpaired data. Id. By using the Wilcoxon method, he got a significant P value (statistical significance), which he would not have gotten with the Mann-Whitney method. Id.

Dr. Zweiman testified there is no molecular mimicry in IDDM. Tr. at 452. When Jonathan had a swollen leg after vaccination, this indicated inflammation. But the chemotactic factors that attract more cells do not send them to another organ, such as the pancreas. Tr. at 453. A viral

infection is more potent than a vaccination. To have an enhanced effect, a microbe must be in the pancreas at the same time of release of an autoantigen. Tr. at 454. This is highly unlikely.

Dr. Zweiman testified that a four-week-old NOD mouse is not analogous to a four-week-old human. Mice are more immunologically competent than people. Tr. at 455. Dr. Ethan Shevach, who was Dr. Classen's supervisor at NIH, said that Dr. Classen does not know what he is talking about. Tr. at 457. Dr. Shevach is one of the outstanding cellular immunologists in the United States. Tr. at 448.

Dr. Zweiman said he does not know the cause of IDDM. Tr. at 458. IDDM is an autoimmune disease for which people are genetically predisposed. Id. It is unknown what begins an autoimmune disease.

There is no evidence for Dr. Classen's hypothesis of causation. Dr. Zweiman finds Dr. Classen's application for patents taints his line of reasoning, interpretation of data, and conclusions because Dr. Classen has a commercial interest. Tr. at 467, 471. There is a hygiene hypothesis to explain why IDDM is increasing in the world. Tr. at 504. This predicates that early treatment for infections skews the immune response from Th1 to Th2. Tr. at 504-05.

Dr. Barry Bercu testified next for respondent. Dr. Bercu is a pediatric endocrinologist, and has practiced for 29 years. He is board-certified in both pediatrics and pediatric endocrinology. Tr. at 475. He sees patients, does research, and teaches. He is chair of an institutional review board, overseeing biomedical research at his university. At NIH for seven years, he created their pediatric endocrinology training program. Tr. at 472-74. He has patents, but does not list them as publications on his CV. Tr. at 478.

The cause of IDDM is multifactorial. Tr. at 482. Fifty percent of the cases of IDDM are due to genetic reasons. In identical twins, if one twin has IDDM, the other twin has a 30 to 50% chance of developing it. Id. We do not have the answers for the cause of IDDM. Tr. at 483. Scientists have looked at viruses. The occurrence of IDDM is seasonal. More cases occur in winter. Tr. at 484. It takes years to develop IDDM because you need to destroy 90% of the pancreatic islet function. Tr. at 484-85.

The increased incidence of IDDM is real in both developed and non-developed countries. Tr. at 486. In Dr. Bercu's opinion, there is no relationship between vaccinations and IDDM. Tr. at 488. The basis for his opinion is his understanding of diabetes, the usual autoimmune disorder, epidemiology, and immunology. Id.

Diabetes is a common disorder. We do not have evidence for what causes it other than genetic susceptibility. Autoimmune disease is common in endocrinology. We do not see an increase in other autoimmune diseases after vaccinations. Tr. at 490. He would expect if vaccines cause one autoimmune disease, they would cause others. Id.

Jonathan Baker does not have any relatives with IDDM. Tr. at 513. An environmental factor could have played a part in his IDDM. Tr. at 513-14. There is no evidence that DPT causes IDDM. There is no biological plausibility. Tr. at 518.

Dr. Classen resumed his testimony and stated he attempted to show through a small sample size a trend. Tr. at 528-29. But Dr. Halsey said that the Finnish data was not a small sample size. The study had sufficient power, but there was no statistically significant difference between the four-dose and one-dose groups in the incidence of IDDM. Tr. at 530. Statistical significance has importance in a study of sufficient power. Tr. at 531. Dr. Halsey stated that Dr. Classen should have

used the two-tailed test in the four-dose versus unimmunized comparison, and his results would not have been statistically significant. Tr. at 549. The one-tailed test makes the numbers smaller and more significant. Tr. at 550.

Dr. Halsey testified that the comparison of the four-dose and one-dose groups shows no statistical significance in the incidence of diabetes. But even if you compared the four-dose group with the unimmunized children, there were a lot of missing P values in Dr. Classen's analysis. If one calculated those, one would find they were not statistically significant. Dr. Halsey stated that if someone were being straightforward about all the data, he would show not just those data selectively in support of his argument, but all the data. Tr. at 583. The numbers that are statistically significant that Dr. Classen shows are by his use of the one-tailed test. He should have used the two-tailed test which would have resulted in their not being statistically significant. Tr. at 583-84. It is inappropriate to pick multiple different points in time and then pick the one analysis that supports one's argument, while ignoring the others. Tr. at 584.

Dr. Classen does not know what causes diabetes in children who are 3, 6, and 8 months of age. Tr. at 565-66. Dr. Classen erased the curves from the graph that Dr. Tuomilehto faxed him and redrew them on new axes. Tr. at 580-82. Dr. Halsey said that this changed the angles and the curves. Tr. at 580. Dr. Classen's analysis of the data shows that 340 per 100,000 developed diabetes in the unimmunized group, 394 out of 100,000 developed diabetes in the four-dose group at 7 years, and 398 out of 100,000 developed diabetes in the four-dose group at 10 years. Tr. at 592. He did not tabulate that information in his paper. Tr. at 594.

Written Submissions

Petitioner filed Exhibit 16, which is Dr. John Barthelow Classen's CV. Petitioner's Exhibit 44 is also Dr. Classen's CV. He lists after his name MD and MBA. He received his MD in 1988 (with an award for excellence in anatomy) and his MBA in 1992. As an undergraduate, he majored in zoology. He also lists his high school and elementary school. He is not board-certified in anything. In 1997, he received a certificate in internal medicine and, since then, has practiced in an urgent care setting, doing repair of lacerations, reading trauma x-rays, splinting fractures, and general medical/pediatric care. He states he sees up to 46 patients daily during 12-hour shifts. Since August 1991, he has been the CEO and sole employee of Classen Immunotherapies, Inc., which he describes as a small biopharmaceutical company that has developed vaccine technology to prevent type I diabetes and autoimmune diseases. He is also a biopharmaceutical consultant and stock analyst for Prudential Securities, Paramount Capital Asset Management, Harmonic Research and others. From 1988 to 1991, he was a staff fellow in the laboratory of immunology, at NIAID, part of NIH. Under publications, he lists five patents or patent applications. He lists letters interspersed with articles, among them 17 co-authored with his first cousin, Dr. David Carey Classen (the overwhelming number being letters).

Petitioner filed Exhibit 98, which is Dr. David Carey Classen's CV. He is board-certified in internal medicine and infectious diseases. He is an associate professor in the Department of Medicine at the University of Utah as well as an infectious disease physician at LDS Hospital in Salt Lake City. The only article which he lists that he has co-authored with Dr. John Barthelow Classen is "The timing of pediatric immunization and the risk of insulin-dependent diabetes," in 6 *Infect Dis in Clin Prac* 449-54 (1997). Most of Dr. David Classen's 49 articles deal with infections. Under

his letters, he does not list any letters that he co-authored with Dr. John Barthelow Classen. The letters also mainly deal with infections.

Petitioner filed Exhibit 21, "Vaccines and the risk of insulin-dependent diabetes (IDDM): potential mechanism of action," by J.B. Classen and D.C. Classen, 57 *Medical Hypotheses* 5:532-38 (2001). They state that immunization at birth is associated with a decreased risk of IDDM while immunization starting after two months is associated with an increased risk of IDDM. They consider molecular mimicry, vaccine-induced alpha interferon release, vaccine-induced lymphokines other than alpha interferon, T helper lymphocyte ratios, macrophages, the adjuvant effect, and increase in autoantibody titers as mechanisms of causation. They conclude that "lack of full comprehension of the mechanisms of action does not detract from toxicology data linking vaccines to IDDM nor does a complete knowledge of the mechanism of action need to be known before studying the potential benefits of new immunization schedules." Id. at 536.

Petitioner filed Exhibit 23, "Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (HiB) Immunization Support Causal Relationship Between Immunization and IDDM," by John Barthelow Classen and David C. Classen, 35 *Autoimmunity* 4:247-53 (2002). The authors claim that HiB vaccine caused IDDM in Finland. They took the data from Finland on all children born between October 1, 1985 and August 31, 1987 (116,000), of whom some received four doses of HiB starting at three months of age (at 3, 4, 6, and 18 months) or one dose starting at 24 months of life. The control group was all 128,500 children born in Finland in the two years prior to the HiB vaccine study. The initial study was limited to seven years, but the authors here extended it to 10 years. They also immunized non-obese diabetic prone (NOD) mice with HiB, hepatitis B, DPaT, and IVP to determine if they increased their risk

of IDDM, which they discovered they did. The control mice received saline solution. The authors used the Wilcoxon test on the animal data. They conclude the vaccinated animals developed IDDM at a higher rate than the control group. As for humans, the authors conclude there is a statistically significant association between HiB vaccine and IDDM up to 7 years. They found clusters of IDDM in that 5-9 age group. The delay in onset between HiB vaccination and development of IDDM was at least three years. They suggest that those studies holding the opposite conclusion be pooled to reach statistical significance in favor of their own conclusions since they believe those other studies' data support their conclusions. Id. at 252.

The authors hypothesize that one of the several mechanisms by which HiB vaccine causes IDDM is the activation of macrophages which destroy islet cells. Vaccine adjuvants, including aluminum and complex polysaccharides, stimulate macrophages. They suggest limiting HiB vaccination to one dose or administering it during the first month of life when it would decrease the risk of IDDM.

Petitioner filed Exhibit 33, "Mumps Infections in the Etiology of Type 1 (Insulin-Dependent) Diabetes," by H. Hyöty, et al., 9 *Diabetes Research* 111-16 (1988). The number of diabetic cases increased significantly two to four years after a mumps epidemic in Finland.

Petitioner filed Exhibit 34, "Is mumps virus an etiologic factor in juvenile diabetes mellitus? Preliminary Report," by H.A. Sultz, et al., 86 *The Journal of Pediatrics* 4:654-56 (1975). The authors strongly encourage further investigation.

Petitioner filed Exhibit 39, "Brief Genetics Report. A Common Stromal Cell-Derived Factor-1 Chemokine Gene Variant is Associated With the Early Onset of Type 1 Diabetes," by D. Dubois-Laforgue, et al., 50 *Diabetes* 1211-13 (2001). The authors state:

> Type one diabetes is an autoimmune disease that is clinically heterogeneous with regard to the great variability of age at onset, its possible association with organ-specific autoimmune diseases, and its occurrence as a sporadic or a familial disease. The genes involved in susceptibility to type 1 diabetes remain largely unidentified. Apart from major histocompatibility complex (MDC) class II genes (IDDM1) and the insulin gene region (IDDM2), many other putative loci have been proposed but not confirmed by recent genome scan studies. Genetics may also influence the rate of progression of the aggressiveness of the disease. [citations omitted.]

Id. at 1211.

Petitioner filed Exhibit 40, "Differential Expression of CC Chemokines and the CCR5 Receptor in the Pancreas Is Associated with Progression to Type I Diabetes," by M.J. Cameron, et al., 165 *Journal of Immunology* 1102-10 (2000). The authors state:

> Nonobese diabetic (NOD) mice spontaneously develop a form of type 1 diabetes that shares many features of the human disease. Mononuclear cell infiltration of pancreatic islets and the progressive TH1 cell-mediated destruction of insulin-producing ß cells herald the onset of autoimmune type 1 diabetes. [citations omitted.]

Id. at 1102.

Petitioner filed Exhibit 41, "Rapid Publication. Identification of Novel Cytokine-Induced Genes in Pancreatic ß-cells by High-Density Oligonucleotide Arrays," by A.K. Cardozo, et al., 50 *Diabetes* 909-20 (2001). The authors state, at 909:

> Type 1 diabetes is an autoimmune disease characterized by the destruction of insulin-producing ß-cells in the pancreatic islets of Langherhans. In both human and rodent models of type 1 diabetes, the clinical disease is preceded by a progressive mononuclear cell invasion of the islets (insulitis), which persists for several weeks/months before significant ß-cell dysfunction and death. Studies in autoimmune diabetes-prone NOD mice and Biobreeding rats indicate that ß-cell destructive insulitis is associated with increased expression of proinflammatory type 1 cytokines, such as interleukin (IL)-1ß, tumor necrosis factor (TNF)-α, and interferon (INF)-γ. [citations omitted.]

The authors also state, at 2001:

> ...ß-cells are not passive bystanders of their own destruction. They respond to immune-mediated damage by triggering complex patterns of gene expression, with some of these genes aggravating ß-cell damage, whereas others probably contribute to cell defense/repair. At some point in this response, the balance is tilted toward ß-cell death. [reference omitted.]

Petitioner filed Exhibit 52, "Hypothesis. The Timing of Pediatric Immunization and the Risk of Insulin-Dependent Diabetes Mellitus," by David C. Classen and John Barthelow Classen (the only co-authored work with John Barthelow Classen that David C. Classen included in his CV), 6 *Infectious Diseases in Clinical Practice* 449-54 (1997). They posit that timing of vaccination can either protect against the development of IDDM (i.e., vaccination at birth) or cause it. The authors state:

> Vaccines cannot explain all of the variability in the incidence of IDDM, and changes in other factors beside vaccines may be responsible for the above-described alterations in the incidence of IDDM. Natural infections with agents such as coxsackievirus B and other viruses may be responsible for the yearly variations in the development of diabetes. Social factors altering exposure to natural infections may be responsible for temporal and geographic differences in the incidence of IDDM. These potential effects, including income, population density, hygiene, caesarean birth, and early enrollment in day care, have been reviewed recently. Consumption of milk and changes in breast-feeding have been associated with geographic and temporal differences in the incidence of IDDM. Variation in temperature–in particular, a higher incidence of IDDM in northern compared with southern countries–has been proposed as an explanation for difference in IDDM incidence in different countries; however, yearly changes in temperature may explain annual variations. Genetic predisposition to IDDM–in particular, the presence of high-risk major histocompatibility complex genes–has been cited as an explanation for geographic differences in the incidence of IDDM. Maternal age has been associated with IDDM, and difference in maternal age because of cultural factors and temporal social factors may also explain difference in the incidence of IDDM. Underreporting of cases of IDDM during previous decades and in countries with less-developed public health care systems cannot be ruled out as a cause for differences in the incidence of IDDM.

Id. at 453.

Petitioner filed Exhibit 55, a draft of an article entitled "Clustering of cases of IDDM occurring 2-4 years after vaccination is consistent with clustering after infections and progression to IDDM in autoantibody positive individuals," by John Barthelow Classen and David C. Classen. On page 39 is Figure 2, a table labeled "Incidence of type 1 diabetes correlates with pertussis immunization rates in UK." The table shows vertical bar columns of incidence of IDDM, compared with rate of immunization four years before. The cumulative incidence of IDDM is per one million people. In 1978, 85 per million people had IDDM, when, four years before, in 1974, 77% were immunized. In 1980, the rate of IDDM incidence rose to 95 per million even though, four years before, in 1976, the percentage of pertussis immunization dropped to 60%. In 1982, the rate of IDDM incidence resumed the 1978 85 per million rate, even though, four years before 1982, in 1978, the rate of immunization dropped further to 37%. According to the table, the rate of immunization never reached the level of 77% as it had been in 1974. But the rate of IDDM rose to 120 per million in 1989 with a vaccination rate of 67% in 1985. Over a span of 11 years, therefore, the rate of immunization fell from 77% in 1974 to 67% in 1985, but the incidence of IDDM rose from 85 per million in 1978 to 120 per million in 1989.

Petitioner filed Exhibit 59, "Rising incidence of insulin dependent diabetes in children aged under 5 years in the Oxford region: time trend analysis," by S.G. Gardner, et al., 315 *BMJ* 713-17 (1997). The authors found an annual increase of 4% from 1985 to 1996 of IDDM. This was due mainly to a rapid increase in children aged 0 to 4 years of age who had an annual increase of 11%. They stated that the cause of the increase was unknown, but environmental influences such as infections with rubella or Coxsackie virus before birth or in early postnatal life were most likely

responsible. They note, at 715, that Finland has the highest incidence in IDDM in the world and has seen a steep increase in children aged under 5 since the mid-1980s.

Petitioner filed Exhibit 60, "The Epidemiology of Type 1 Diabetes in Children in Philadelphia 1990-1994. Evidence of an epidemic," by T.H. Lipman, et al., 25 *Diabetes Care* 11:1969-75 (2002). The authors found that Hispanic children had the highest incidence of IDDM among any racial group in this country, which also manifested in Puerto Rico. They posit that their higher incidence may be due to a combination of genetic and environmental risk factors. In Philadelphia, the incidence of IDDM in African-American children continued to be rare among 0 to 4 year olds. However, in the African-American children aged 10-14 years, the incidence of IDDM rose dramatically to almost equal the white population. This was true in Chicago and Allegheny County as well.

Petitioner filed Exhibit 67, "Association between type 1 diabetes and *Haemophilus influenzae* type b vaccination: birth cohort study," by M. Karvonen, Z. Cepaitis, and J. Tuomilehto, 318 *BMJ* 1169-72 (May 1, 1999). The authors compared the incidence of IDDM in children born from 1983 to 1985 before HiB immunization was instituted with those vaccinated with HiB at the age of 2 years who were born on even days from 1985 to 1987 and found no statistically significant difference. There was also no statistically significant risk between those vaccinated first at the age of 3 months (and received four doses ultimately) and those vaccinated at 2 years (and received one dose). The authors conclude that HiB is unlikely to cause IDDM in children. Each child was followed for 10 years. The risk of diabetes was not influenced by either vaccination with HiB or timing (3 months or 2 years). The incidence of IDDM in Finland is the highest in the world, and its incidence has been increasing by 2-3% per year since the mid-1960s. Id. at 1171. The increase has been virtually linear

since 1965. The authors state "it is very likely that the incidence was already increasing in Finland before the first nationwide childhood immunisation programme, with BCG vaccine, was started in 1941." Id.

Petitioner filed Exhibit 68, "Record-high incidence of Type I (insulin-dependent) diabetes mellitus in Finnish children," by J. Tuomilehto, et al., 42 *Diabetologia* 655-60 (1999). Finland has had the highest incidence of IDDM in the world for the last two decades. From 1987 to 1992, the incidence was 37 for 100,000 years for boys and 32 for 100,000 person years for girls (or 36 per 100,000 person years). There were peaks of 38 per 100,000 person years in 1986 and 39 per 100,000 person years in 1991. Since 1994, the incidence has been over 40 per 100,000 person years. In 1996, it was 45 per 100,000 person years. There have also been increases reported in Sweden, Norway, Holland, Austria, Hungary and England. A major increase was reported in Kuwait. Id. at 658. Genetic effects explain 70-75% of the susceptibility to Type I diabetes. Id. Environmental effects may explain the rest. Finland is the first country to have an incidence of IDDM of greater than 40 per 100,000 person years. The incidence will surpass 50 per 100,000 person years in 2010, and 55 per 100,000 person years in 2020. The only other population to reach a level of 30 per 100,000 person years is in Sardinia. Id. at 659.

Petitioner filed Exhibit 78, "Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus," by F. DeStefano, et al., 108 *Ped* 6:1-5 (December 2001). The authors conducted a case-control study within 4 HMOs that participated in the Vaccine Safety Datalink project of the CDC. The children were born between 1988 and 1997. They attempted to match 3 controls per diabetic child. There were a total of 252 confirmed cases of IDDM and 768 matched controls. The odds ratio for association of IDDM and HiB was 0.81. The authors concluded that

there was no increased risk of IDDM associated with any of the routinely recommended childhood vaccines (DPT, MMR, HiB, varicella, DPaT, hepatitis B). "Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded." Id. at 1. They state:

> Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus or juvenile diabetes) results from autoimmune destruction of pancreatic β-cells. Its cause is not known, although genetic and environmental factors are believed to be involved. Vaccinations are among the environmental factors that have been studied, but most studies have not found an increased risk of type 1 diabetes associated with vaccination. [citing 7 papers by Blom, Hyoty, Dahlquist, Parent, Heijbel, Jefferson, and the Institute for Vaccine Safety Workshop Panel.]

Id.

The authors discuss the Classen papers. Id. at 2. They state,

> Classen has provided the only evidence of a possible increased risk, but the nature of the evidence is strictly ecological, involving comparisons between countries or between different time periods in the same country. Such comparisons, however, may be influenced by many factors unrelated to vaccination, such as genetic predisposition and other environmental exposures. Moreover, similar ecological analyses conducted by other investigators have not found significant correlations between diabetes and several vaccines, including BCG, pertussis, and mumps. [citations omitted.]

Id. at 4. They continue, "None of the epidemiologic studies that included control or comparison groups have found an increased risk of type 1 diabetes associated with vaccination." Id. They go on to discuss one of the largest and most comprehensive studies arising from Sweden. The only significant difference between cases and controls was a decreased risk of type 1 diabetes associated with measles vaccination. The DeStefano study adds to previous research by including newer vaccines, including hepatitis B, acellular pertussis, and varicella vaccines. "For the older vaccines, our results are generally in agreement with previous studies in not finding any increased risks." Id.

The authors believe that theirs is the first epidemiologic study to evaluate the possibility that timing of vaccination is related to the risk of IDDM in children. Classen suggested that vaccination at birth to two months of age would decrease the incidence of IDDM, but if vaccination occurs after two months of age, the incidence increases. Classen based his theories on laboratory animal experiments and comparisons of the rates of diabetes between countries with different immunization schedules. DeStefano's results on hepatitis B vaccine do not support Classen's hypothesis. Risk of IDDM did not differ between infants vaccinated at birth and those who received their vaccines later.

The authors cite data from the Diabetes Autoimmunity Study which proved that vaccination or timing of vaccination was not associated with the incidence of IDDM. "No association was found between development of β-cell autoimmunity and receipt of any of a number of vaccines, including hepatitis B, Hib, polio, or diphtheria and tetanus toxoids and pertussis; nor was there an association with age at first vaccination with any of these vaccines." Id. at 5. The authors conclude:

> The results of our study and the preponderance of epidemiologic evidence do not support an association between any of the recommended childhood vaccines and in increased risk of type 1 diabetes. Suggestions that diabetes risk in humans may be altered by changes in the timing of vaccinations also are unfounded.

Id.

Petitioner filed Exhibit 79, "Infections and vaccinations as risk factors for childhood Type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation," by The EURODIAB Substudy 2 Study Group, 43 *Diabetologia* 47-53 (2000). Eight centers in Europe provided data on children with IDDM diagnosed under 15 years of age. Id. at 48. There were 900 cases and 2,302 control children. Infections in the months or year preceding diagnosis was more

common in children with IDDM than in control children. There was a seasonal peak in winter. The authors surmised that infections could play a part in precipitating IDDM. There was no evidence that any common childhood vaccination modified the risk of diabetes.

None of the odds ratios for nine vaccines examined was statistically significant. Id. at 49. The authors state that the "possible role" of vaccinations in IDDM continues to be debated, "but there is a lack of reliable data." Id. at 51. "Our study, one of the largest case control studies yet conducted to address this issue, found no evidence to support vaccination modulating the risk of childhood diabetes." Id. They also did not find that early BCG vaccination was protective against the development of IDDM. Id.

Petitioner filed Exhibit 80, "Lack of Association Between Early Childhood Immunizations and β-Cell Autoimmunity," by P.M. Graves, et al., 22 *Diabetes Care* 1694-97 (1999). The authors attempted to determine if changing the schedule for early childhood immunization with hepatitis B, HiB, polio and DPT would affect the risk of developing the β-cell autoimmunity that precedes IDDM. They found that changing the schedule did not alter the risk. The authors' first three citations for the proposition that vaccinations before the age of two months would alter the risk are to articles that Dr. Classen wrote. The last of these citations to Dr. Classen is his Finnish analysis suggesting that immunizing with HiB at the age of two years results in less of a risk of IDDM than starting HiB vaccination at age 3 months as part of a four-dose series. Id. at 1694.

The authors also discuss two Finnish reviews that find no difference in the rate of IDDM among groups not vaccinated, given one dose of HiB at 24 months, or four doses of HIB starting at age three months. In their case-control study, the authors evaluated the effect of timing and dose of hepatitis B and HiB vaccine, as well as polio and DPT, on the development of β-cell autoimmunity

in children at high risk for developing IDDM. They were at high risk because they had a first-degree relative with IDDM. The authors state that no difference was observed between cases and control subjects, suggesting that the timing of immunization did not affect the risk of β-cell autoimmunity. Id. at 1696. They cite to a German study by Hummel whose results were the same. They cite to two articles by Jefferson that vaccinations have no relationship to the incidence of IDDM.

Petitioner filed Exhibit 83, Immunization Safety Review. Multiple Immunizations and Immune Dysfunction by K. Stratton, et al., Institute of Medicine (IOM) (National Academy Press, 2002), pp. 55-67. The authors reviewed all the medical literature, including Dr. Classen's articles. Referring to Dr. Classen's article on hepatitis B vaccinations in New Zealand, the authors discuss Dr. Classen's proposed possible link between hepatitis B vaccine and the rising incidence of IDDM. The children were also routinely immunized with DPT, MMR, and OPV. Dr. Classen did not make any control "for the general secular trend of increasing diabetes incidence rates." Id. at 55. The authors of the IOM study concluded that "the ecological nature of the study limits the ability to make inferences about causation." Id. at 56.

The IOM authors discuss Dr. Tuomilehto's paper, calling attention to the fact that comparing his three cohorts produced a relative risk of only about 1.0 (comparing the one-dose group to the unimmunized and comparing the four-dose group to the one-dose group). They discuss a Swedish study dealing with whether DPT affects the risk of developing IDDM and finding in the negative. In another Swedish study, the authors concluded that the evidence did not support an increased risk of IDDM after vaccination, and measles vaccine might protect against IDDM. Id. at 62. The IOM authors conclude "that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes." Id. at 63.

Petitioner filed Exhibit 84, "Decline of mumps antibodies in Type 1 (insulin-dependent) diabetic children and a plateau in the rising incidence of Type 1 diabetes after introduction of the mumps-measles-rubella vaccine in Finland," by H. Hyöty, et al., 36 *Diabetologia* 1303-08 (1993). The elimination of mumps disease through the use of MMR vaccine may have decreased the risk for IDDM in Finland. Diabetic children had a decrease in mumps antibody levels. The authors suggest further studies to determine if the attenuated virus in MMR could trigger the clinical onset of IDDM. As they state in 1993, "the question remains open." Id. at 1307.

Petitioner filed Exhibit 85, "The Swedish childhood diabetes study. Vaccinations and infections as risk determinants for diabetes in childhood," by L. Blom, et al., 34 *Diabetologia* 176-81 (1991). The authors found a protective effect from measles vaccine on the development of IDDM in childhood. They also found a relationship between infections and the onset of IDDM.

Petitioner filed Exhibit 86, "Current Opinion. Immunisation and Type 1 Diabetes Mellitus. Is There a Link?" by M. Hiltunen, et al., 20 *Drug Safety* 3:207-12 (Mar. 1999). The authors conclude, after reviewing literature and animal studies, that there is no clear evidence that vaccines prevent or induce IDDM. They state, "The incidence of type 1 diabetes mellitus shows a constant linear increase which is difficult to explain by the effect of any single vaccine implemented during the last 20 years in Finland." Id. at 210. Even though the authors reviewed studies that Dr. Classen had written, they conclude:

> No further conclusions can be drawn concerning the link between immunisation and type 1 diabetes mellitus based on the studies that have been currently performed on the topic. There is no clear evidence that any vaccine could induce type 1 diabetes mellitus in humans....

Id. at 211.

Petitioner filed Exhibit 87, "Risk factors for type I diabetes mellitus in children in Austria," by B. Rami, et al., 158 *Eur J Pediatr* 362-66 (1999). They found that the development of IDDM was associated with higher paternal age and neonatal jaundice, but they found no correlation with intake of cow's milk in early infancy, vaccination or other environmental factors.

Petitioner filed Exhibit 88, "Cumulative Incidence of Childhood-Onset IDDM Is Unaffected by Pertussis Immunization," by H. Heijbel, et al., 20 *Diabetes Care* 2:173-75 (Feb. 1997). The authors begin their article by discussing Dr. Classen's suggestions that vaccination after 2 months of age results in an increased incidence of IDDM. By comparing children with a high rate of vaccination to children with a low rate in Sweden, the authors found no support for the thesis that DPT induces autoimmunity to the β-cell that may lead to IDDM.

Petitioner filed Exhibit 89, "A Brief Original Contribution. Incidence of Insulin-dependent Diabetes Mellitus in Young Adults: Experience of 1,587,630 US Navy Enlisted Personnel," by E.D. Gorham, et al., 138 *Amer J Epidem* 11:984-87 (1993). The authors found a higher rate of IDDM among black men than among white.

Petitioner filed Exhibit 90, "Variation and trends in incidence of childhood diabetes in Europe," by EURODIAB ACE Study Group, 355 *Lancet* 873-76 (2000). The authors found a very wide range of incidence rates of IDDM in Europe which varied from country to country. There was rapid rate of increase in children under the age of 5 years. They surmised that "exposures operating early in life," such as increased perinatal infections or a rapid growth rate in early life, may be contributing factors. Id. at 875.

Petitioner filed Exhibit 95, which includes a summary of what appears to be a presentation at a conference, "Hepatitis B and Hib Vaccines are not Associated with Increased Risk of Type 1

Diabetes," by F. DeStefano, et al., 40th ICAAC (2000). They used the diabetes registries from four HMOs to identify all children with diabetes born since 1988. Three controls were matched to each case. They estimated relative risks of IDDM and HiB as 0.88 and of IDDM and hepatitis B vaccine as 0.81. They conclude that HiB and hepatitis B vaccines are not associated with an increased risk of IDDM. In addition, timing of hepatitis B vaccination is not associated with an increased risk of IDDM.

Petitioner filed Exhibit 97, which includes "Childhood immunizations and type 1 diabetes: summary of an Institute for Vaccine Safety Workshop," by The Institute for Vaccine Safety Diabetes Workshop Panel,[8] 18 *Pediatr Infect Dis J* 3:217-22 (1999). To address concerns raised in the media over the relationship between vaccinations and IDDM, the Institute for Vaccine Safety at the Johns

[8] The 21 workshop panel members were: Dr. Elaine Collier (Chief of Autoimmunity, National Institutes of Health [NIH]); Dr. Frank DeStefano (CDC, Vaccine Safety and Development Activity, National Immunization Program); Mark S. Eberhardt, Ph.D. (National Center for Health Statistics); William M. Egan, Ph.D. (Deputy Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA); Susan Ellenberg, Ph.D. (Director, Division of Biostatistics and Epidemiology, FDA); Dr. Michael Engelgau (Medical Epidemiologist, Division of Diabetes Translation, CDC); Dr. Geoffrey Evans (Medical Director, National Injury Compensation Program); Dr. Bruce G. Gellin (Infectious Diseases Society of America Vaccine Initiative); Patricia Graves, Ph.D. (Department of Preventive Medicine and Biometrics, University of Colorado Health Science Center); Charles J. Hackett, Ph.D. (Chief, Molecular and Structural Immunology Section, NIH); Dr. Neal A. Halsey (Director, Institute for Vaccine Safety, Johns Hopkins University); Maureen I. Harris, Ph.D. (Director, National Diabetes Data Group, NIH); Ronald E. LaPorte, Ph.D. (Professor, Department of Epidemiology, University of Pittsburgh); Dr. Noel K. Maclaren (Research Institute for Children, Louisiana State University Medical Center); Lawrence H. Moulton, Ph.D. (Co-Director, Institute for Vaccine Safety, Johns Hopkins University); Dr. Regina Rabinovich (Chief, Clinical Studies Section, Division of Microbiology and Infectious Diseases, NIH); Dr. Noel R. Rose, MD (Professor, Department of Molecular Microbiology and Immunology, Johns Hopkins University); Dr. Christopher D. Saudek (Director, Johns Hopkins Diabetes Center); Stephen J. Sepe, M.P.H. (Associate Director, National Vaccine Program Office); Kathleen R. Stratton, Ph.D. (Director, Division of Health Promotion and Disease Prevention, IOM); and Elaine Young, Ph.D. (Juvenile Diabetes Foundation, Int.).

Hopkins School of Public Health held a workshop on March 20, 1998 in Baltimore, MD to review the available information, including Dr. Classen's work. Workshop participants included experts on the pathogenesis of diabetes, autoimmunity, epidemiology, biostatistics, vaccines, and adverse events associated with vaccines. Id. at 217. Among their conclusions, the Workshop Panel concluded that no vaccines have been shown to increase the risk of IDDM. Id.

Factors associated with an increased risk of developing IDDM include genetic factors. There are different rates of the disease in different racial and ethnic groups. Dr. Ronald LaPorte presented data showing a 35-fold difference in the incidence of IDDM in different populations. There was a 12-fold difference in China. Id. at 217-18. More IDDM occurs in colder climates, possibly due to increased cold stress and demands on pancreatic islet cells. Other autoimmune disorders, such as multiple sclerosis, have similar patterns. Id. at 218. Breast milk may be protective, while the data for cow's milk is inconclusive. Id.

Congenital rubella syndrome can increase the risk of IDDM in humans. Id. Enteroviruses may be related to the risk of IDDM. A recently identified human retrovirus may also lead to IDDM. Viral infection may explain peaks in the incidence of IDDM. Id. There is a slight seasonal pattern in the onset of IDDM, peaking in the summer and early fall months, which is also the peak season for enterovirus. Id.

In animals, some vaccines may have a protective effect on the risk of developing IDDM, but the data for humans is inconsistent and inconclusive. "There is no evidence that any vaccines have increased the risk of type 1 diabetes in animals or humans." Id. at 219. They discuss Dr. Classen's work, stating that "ecological studies do not demonstrate causal relationships. Several other factors

could explain the observed differences in diabetes including genetic differences in populations and increased exposure to immune modulating infections early in life in tropical climates." Id.

Reviewing Dr. Classen's analysis of the Finnish data and his claim that children who received one dose of HiB had a lower incidence of IDDM than those who received four doses, "the panel concluded that **the analytic methods were incorrect** and a careful analysis of data from 10 years of follow-up has revealed no significant differences in the incidence of type 1 diabetes mellitus in children who received one *vs.* four doses of Hib vaccine (J. Tuomilehto, personal communication) [emphasis added]." Id

Dr. LaPorte presented data demonstrating a global increase in the incidence of IDDM. The Workshop Panel states:

> Because the incidence of type 1 diabetes mellitus has increased in countries with and without introductions of new vaccines into the immunization schedule, the data do not support the hypothesis that vaccines affect the risk of diabetes mellitus. Dr. LaPorte obtained additional preliminary data from other diabetes investigators who have conducted case-control studies. None of their studies revealed significant differences in rates of receiving any vaccine in children with type 1 diabetes as compared to controls.

Id. at 219-20.

Dr. Patricia Graves presented data from a prospective cohort study (DAISY) of children at high risk for developing IDDM and found no difference in their early childhood immunization histories compared to controls. A New Zealand study by J. Willis, et al., showed no association between hepatitis B vaccine and IDDM. Id. at 220.

Petitioner filed Exhibit 99, a letter entitled, "Vaccines and their real or perceived adverse effects. Authors' conclusions are at odds with investigators'," by T.O. Jefferson, R. Rabinovich, and

J. Tuomilehto, 318 *BMJ* 1487-89 (May 29, 1999). They state that Dr. Classen's conclusions about the risk of IDDM from early immunization are at odds with the analyses and conclusions of the Finnish investigators' and they suggested that Dr. Classen's analysis be sent to an independent statistician, but this was not done. The Workshop Panel indicated concern about Dr. Classen's methodology in statistical analysis and his design and conduct of the studies. They also note:

> Dr. J.B. Classen has filed a European and American patent on his schedule that may have widespread implications should his views be implemented. He applies for a patent on immunisation schedules to be administered from birth, both to reduce the likelihood of type1 diabetes developing and to protect individuals from communicable diseases. The safety or efficacy of one particular paediatric schedule (annex 5 of the application) has not been shown. [citations omitted.]

Id. at 1489.

Respondent filed Exhibit H-4, "Editorials. Vaccination and its adverse effects: real or perceived. Society should think about means of linking exposure to potential long term effect," by T. Jefferson, 317 *BMJ* 159-60 (July 18, 1998). He reviews the findings of the Workshop Panel. Dr. J. Tuomilehto reanalyzed the Classen findings and "showed no association between the incidence of diabetes mellitus and the addition of another antigen to the schedule, irrespective of timing (unpublished data)." Id. at 159.

Respondent filed Exhibit H-6, "Review Article. Mechanisms of Disease. Molecular Mimicry and Autoimmunity," by L.J. Albert and R.D. Inman, 341 *New Eng J Med* 27:2068-74 (Dec. 30, 1999). The authors state, "No data convincingly demonstrate that mimicry is an important mechanism in the development of autoimmune disease in humans." Id. at 2073.

Respondent filed H-9, "No evidence that vaccines cause insulin dependent diabetes mellitus," by T. Jefferson and V. Demicheli, 52 *J Epidemiol Community Health* 674-75 (1998). The authors

discuss Dr. Classen's hypothesis. They examined 54 studies and interviewed eight researchers active in investigating trigger factors for IDDM. They reviewed a sample of 12 large trials and two meta-analyses of pediatric vaccines. They found that international analytical literature is insufficient and too limited to prove a link between vaccination and IDDM. There was no evidence in human. "The papers that explored the relation between vaccination and IDDM either did not find evidence of the causal link or found evidence against such a link." Id. at 675.

Respondent filed H-10, a letter entitled, "Hepatitis B vaccination and diabetes," by H. Petousis-Harris and N. Turner, *New Zealand Med J* 303-04 (Aug. 13, 1999). The authors state that Dr. Classen's website uses New Zealand data to support his hypothesis that hepatitis B vaccine is related to IDDM. He discussed this relationship before Congress. The letter's authors state that the NZ data do not support his theory. The cases of IDDM have increased wtih time since 1970, peaking in 1990. Hepatitis B vaccine was introduced in 1988, replaced by recombinant vaccine one year later. The cumulative incidences of IDDM were 6.8 in the unimmunized and 6.4 in those immunized at birth. This does not provide evidence that hepatitis B causes IDDM. Hepatitis B vaccine introduction in the Auckland area did not alter the steady pattern of increased incidence of IDDM. The increased incidence of IDDM is "entirely explained by the secular diabetes rate increase." Id. at 303.

Respondent filed Exhibit I-8, "Vaccination and type 1 diabetes mellitus. Currently no evidence of a link, but more studies are needed as vaccines change," by D. Ellman, 318 *BMJ* 1159-60 (May 1, 1999). Commenting on Dr. Classen's hypothesis, Ellman notes the publication of Dr. Tuomilehto's study of Finnish children vaccinated with one or four doses of HiB and unimmunized controls. He states:

> The authors found no statistical difference in the cumulative incidence of diabetes at the age of 10 between the cohorts. This was a well designed and very carefully conducted study whose methodology cannot be criticised, so we can be reassured about the validity of the findings.

Id. at 1160.

Respondent filed Exhibit I-9, "No Major Association of Breast-Feeding, Vaccinations and Childhood Viral Diseases With Early Islet Autoimmunity in the German BABYDIAB Study," by M. Hummel, et al., 23 *Diabetes Care* 7:969-74 (July 2000). The authors assessed the influence of breast-feeding, vaccinations (including DPT, HiB, and MMR), and childhood viral diseases on the development of islet autoimmunity in early childhood. Neither type nor quantity of vaccinations was associated with the development of islet antibodies and IDDM. BABYDIAB is a prospective study from birth in offspring of parents with type 1 diabetes. Id. at 969. Their data was consistent with that from the United States and New Zealand that found no associations between vaccination and IDDM. Id. at 973.

Respondent filed Exhibit U, "Letter to the Editor," by N.A. Halsey, *Autoimmunity* 1 (August 2, 2003). Dr. Halsey criticizes Dr. Classen's conclusion of a relationship between HiB and IDDM:

> The report by Classen and Classen involves the **use of inappropriate methods and reports data that do not provide evidence of a causal association between *Haemophilus influenzae* type B (Hib) vaccine and diabetes.** No statistical methods were provided for the animal studies and the results are presented in smooth, atypical lines. Survival curves reporting data from small numbers usually have a staircase shape. ...
> The reanalysis of the human study **suffers from design flaws and incorrect interpretations.** An increasing incidence of type 1 diabetes has been observed in countries throughout the world, including Finland, before and after the Hib vaccine study. ...
> The investigation of possible differences in the incidence of diabetes in children who received one vs. four doses of Hib vaccine was designed to compare the overall incidence in the two groups. The Finnish investigators who conducted this study have reported that there were no significant

> differences in the incidence of diabetes in children who received one vs. four doses of Hib vaccine at any time during the study. It is inappropriate to look at the data after the study and **arbitrarily** pick a point where the curves appear to diverge and then use that point for comparing the subsequent incidence of disease.
> [T]he use of a one-sided statistical test is inappropriate in a study where the intervention could theoretically increase or decrease the incidence of the outcome disease. There are differences in the two curves in parts a and b of the figure reporting the cumulative incidence of diabetes in children who received one dose of Hib vaccine. Either the data are not from the same study or different methods of analysis or creating the curves were used.
> Careful reviews by three expert panels have concluded that the available evidence does not support Dr. Classen's hypothesis that Hib vaccine contributes to type 1 diabetes. [emphasis added] [citations omitted.]

Id.

Respondent filed Exhibit V, a chapter entitled "Prevalence and Incidence of Insulin-Dependent Diabetes," by R.E. LaPorte, et al., pp. 37-46 from Diabetes in America, 2d ed. (1995). The authors state that there is more than a 50-fold geographic variation in the annual incidence of IDDM, ranging from 0.7 per 100,000 in Shanghai to 35.3 per 100,000 in Finland. In the United States, there is considerable racial and ethnic variation: 3.3 per 100,000 in African Americans in San Diego to 20.6 per 100,000 in whites in Rochester, MN. In the white population that is non-Hispanic, males have a slightly higher incidence rate. For Hispanics and African Americans, the rate is slighty higher in females. The rate of IDDM incidence varies by season, with lower rates in the summer. Europe and several other countries have had an increasing IDDM incidence over time, whereas the incidence in the United States has been stable over the past several decades, except for rapid rises during certain years and in certain areas that may suggest epidemics. Id. at 37. The highest rate of IDDM in the world is in Finland, followed by Sardinia, the US Virgin Islands (among whites),

Sweden, Prince Edward Island, Denmark, and Norway. The least occurrence of IDDM is in Peru, Dar es Salaam, Shanghai, Mexico City, and the Republic of Korea. Id. at 41.

Respondent filed Exhibit W, a letter from Dr. Jaako Tuomilehto. (R. Ex. X is a shortened version of Dr. Tuomilehto's CV.) The letter, dated May 9, 2003 and which the undersigned specifically ordered be produced in an Order dated February 25, 2003, states that Dr. Tuomilehto is not Dr. Classen's collaborator (as Dr. Classen had referred to him during the hearing). Dr. Tuomilehto states:

> We have not omitted any data and endpoints or important information. ... Dr. Classen is proposing an analysis where only a fraction of the available data are used, i.e., certain years during the follow-up, not the entire follow-up data. In medical research such an approach is called "post-hoc analysis" or "subgroup analysis." Such an approach is considered inferior and sometimes misleading, because "statistically significant" findings in such analyses often happen just by chance. Most stringent medical researches never agree to do such analyses, and many medical journals do not accept papers from such analyses to be published. We included the entire 10 years of follow-up in our analyses and the analyses were done using adequate statistical methods. The analyses have been checked also by the CDC in Atlanta and they have agreed that we have done analyses correctly.
>
> It is true that the curves were not different after 10 years, i.e., a similar number of children developed the disease after 10 years in the two groups. Of course one can calculate the difference at every single year. If one does that, then there is the above mentioned subgroup analysis problem. In addition, the estimates for statistical significance between the groups will change since in such a situation 10 comparisons (one comparison each year) instead [of] one comparison will be done. This is called in medical statistics "multiple comparison" problem. If doing for some reason multiple comparisons, one must take this into account and multiply the estimates of statistical significance by factor 10. In Dr. Classen's claim he did not do it. If he would [have] applied proper statistics from this point of view, his "statistical significance" at seven years will be not significant. It seems he is not very well informed about the ways and rules of statistical analysis of the data.
>
> There is no "clustering" of diabetes in our data. The word clustering does not suit to prospective follow-up of a cohort.... [I]t is misused by Dr. Classen here. ... We have clearly documented that there has been virtually linear

> increase in type I diabetes incidence in Finland since 1953 when the first nationwide study in this country was carried out. New vaccination programs introduced in the country at various points in time or other factors that have occurred over time did not show any effect on this linearly increasing trend. An increase in incidence has also been observed in practically all countries where long-term data are available regardless of their vaccination policies or programs.

Dr. Tuomilehto concludes his letter by saying, "It is unfortunate that scientific papers and data are misused and claims made that are not justified by the results." He strongly disagrees that he "would have been involved in scientific fraud. The interpretation of the results from my scientific work are correct as I have written in my publications."

Dr. Tuomilehto's CV (R. Ex. X) shows that he has an MD, M. Pol. Sc., and Ph.D. in Epidemiology and Community Medicine. He was awarded the Kelly West Award for Outstanding Achievement in Epidemiology by the American Diabetes Association in Chicago in 1998. He received the Peter Bennett Diabetes Epidemiology Award from the International Diabetes Epidemiology Group in Acapulco in 2002. He received the UNESCO-Hellmut Mehnert Award on aetiology and prevention of diabetes in Dresden in 2002. Also in 2002, he received the MEDIX award for the most outstanding publication in medical sciences from Finland in 2001.

Dr. Tuomilehto is a member of the advisory board for 12 scientific journals and a reviewer for assessing the scientific qualification of applicants for professorships at seven universities outside Finland. He is a visiting professor or scientist at 20 international institutions. He is Professor of Public Health at the University of Helsinki, Academy Professor at the Academy of Finland, and Visiting Professor of Neuroepidemiology at the Danube-University Krems, Austria.

Dr. Classen responded to Dr. Tuomilehto's letter in one of his own (P. Ex. 108), and states, among other things, that the reason his endpoint of seven years is correct is that he reached statistical

significance. He states, "The object of science is to reach statistical significance not to fail statistical significance!!!" [underlining and exclamation points in letter.] Id. at 2. Dr. Classen regards causes of IDDM that are other than vaccines to be "noise" whereas vaccine causation of IDDM is "signal." Id. Dr. Classen regards CDC's agreeing with Dr. Tuomilehto's analysis to be "moot since the CDC, a branch of the US government, is a defendant in the case." Id. at 3.

Pursuant to an Order dated November 22, 2002, the undersigned asked for a response by Dr. Classen to whether or not he has a conflict of interest in opposing the current vaccine regimen because of his patents on alternative schedules for delivery of vaccines to children.[9] There were Tabs A through J attached to this Order. Tab A is from the December 2000 *Diabetes Interview* by Daniel Trecroci, www.diabetesinterview.com/archive/december/dec2-00print.html:

> Lone researcher J. Barthelow Classen, MD, MBA, is still clinging to his nine-year-old theory that childhood vaccines are the largest cause of type 1 diabetes. The theory, which Classen claims has kept him living in poverty for nine years, has been convincing enough to lead researchers around the world to conduct studies of their own, all of which dispute the findings of Classen.
> On September 19, the U.S. Centers for Disease Control and Prevention (CDC), at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAACC) in Toronto, proclaimed in its latest study there was no increased risk of diabetes associated with the hepatitis B and hemophilus vaccine, regardless of the age at first vaccination.

Id. at 1.

Mr. Trecroci cites Frank Vinicor, MD, MPH, director of the division of diabetes translation at CDC, that there were two international meetings, one at Johns Hopkins and the other at NIH,

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[9] Petitioner filed Dr. Classen's response on January 31, 2003, in which Dr. Classen denies that he will receive financial gain if petitioner prevails. He states that his patents and patent applications fall into three categories, of which only the first two pertain to vaccine litigation. He goes through a lengthy explanation of why his patents will not enrich him, in direct contrast to his answers to Mr. Trecroci in the Diabetes Interview described above.

specifically addressing the questions Classen raised. Both organizations felt there was insufficient evidence to support his conclusion. Dr. Frank DeStefano stated that, based on scientific evidence, someone seeking monetary damage for IDDM as a vaccine injury would have a weak case. Id. at 2.

Mr. Trecroci interviewed Dr. Classen's former supervisor at NIH, Dr. Ethan M. Shevach, chief of cellular immunology at the laboratory of immunology at NIH. "He claims that Classen had very little training in immunology before he arrived and functioned in a satisfactory, but not outstanding way. 'I am familiar with [Classen's] theories, but have never been impressed with any of the data he has presented in public or in the press,' says Shevach. 'He has had absolutely no formal training in sophisticated epidemiologic techniques or methods, and I am not really certain of the reliability of his data-analysis methods.' Shevach believes Classen has a 'rather naive' understanding of basic immunologic principles and theories." Id. at 3.

At a May 1998 meeting, Dr. Classen's website states Dr. Classen alluded to Dr. Shevach's data to support his view that vaccines cause IDDM, and Dr. Classen wrote that Dr. Shevach presented data that certain DNA vaccines probably cause the release of interleukin 14 (IL-14), which can introduce autoimmunity. "Shevach responds by saying this is 'absolute nonsense' and that Classen's Web site is incorrect." Id. at 3-4. Dr. Shevach lectured on the potential of interleuken 12, not IL-14, to induce autoimmunity. IL-14 does not exist. Dr. Shevach stated he does not see any hard scientific data to support any of Dr. Classen's claims that vaccines cause IDDM. "I think he is doing a disservice to the scientific community and to the families of patients with children with type 1 diabetes." Id. at 4. Dr. Shevach thinks that natural infectious insults would be much more potent inducers of potential autoimmunity than injecting a recombinant purified protein as a vaccine.

As to Dr. Classen's claim that 80% of IDDM occurring before age 10 is caused by multiple vaccinations administered after two months of life, Dr. Shevach stated, "This guy simply does not know what he is talking about." Id.

"Adding fuel to the controversy, Shevach charges that Classen has obtain patents on alternative schedules for delivery of vaccines to children and that he has a 'vested financial interest in the use of his protocols. I would question whether he has a conflict of interest,' says Shevach. Classen says he would never deny that he has patents as well as a conflict of interest." Id. Dr. Classen stated to Mr. Trecroci that he believed that his patents are worth money because they are true. "Classen says he has been working in poverty for nine years because, in the end, he feels he will be compensated." Id.

"'You can look at Charles Darwin when he proposed evolution and how the church and everyone else was against him,' says Classen. "Or when Aristotle said the earth rotates around the sun instead of vice versa. Science was on their sides. In the end, science wins out, and that is why I continue. That is why I take on the biggest people, because I know the science will win in the end.'" Id. at 5.

Tabs B through J of the undersigned's Order dated November 22, 2002 describe Dr. Classen's patents and patent applications. Tab B is a patent application for a system for creating and managing proprietary product data. Tab C is a Patent Cooperation Treaty application for improved algorithms and methods for product safety. Tab D is a U.S. patent for a method and composition for an early vaccine to protect against both common infectious diseases and chronic immune-mediated disorders or their sequelae. Tab E is a U.S. pre-grant publication of computer algorithms and methods for product safety. Tab F is a Patent Cooperation Treaty application for a system for

creating and managing proprietary product data. Tab G is a U.S. patent for a system for creating and managing proprietary product data. Tab H is a U.S. patent for a method and composition for an early vaccine to protect against both common infectious diseases and chronic immune-mediated disorders or their sequelae. Tab I is a U.S. patent for a method and composition for an early vaccine to protect against both common infectious diseases and chronic immune-mediated disorders or their sequelae. Tab J is a European patent application for a method and composition for an early vaccine to protect against both common infectious diseases and chronic immune-mediated disorders or their sequelae.

Under 42 U.S.C. § 300aa-12(d)(3)(B)(1), a special master "may require such evidence as may be reasonable and necessary." On February 13, 2003, the undersigned filed C. Exhibits 1 through 8. C. Exhibit 1 is Gale, E.A.M., "The Rise of Childhood Type 1 Diabetes in the 20th Century," pub. in 51 *Diabetes* 12: 3353-61 (2002), but submitted from www.medscape.com. Dr. Edwin A.M. Gale is in the Department of Diabetes and Metabolism, Division of Medicine, University of Bristol, Bristol, UK. He states:

> The incidence of childhood type 1 diabetes increased worldwide in the closing decades of the 20th century, but the origins of this increase are poorly documented. ... Childhood type 1 diabetes was rare but well recognized before the introduction of insulin. Low incidence and prevalence rates were recorded in several countries over the period 1920-1950, and one carefully performed study showed no change in childhood incidence over the period 1925-1955. An almost simultaneous upturn was documented in several countries around the mid-century. The overall pattern since then is one of linear increase, with evidence of a plateau in some high-incidence populations and a catch-up phenomenon in some low-incidence areas. Steep rises in the age-group under 5 years have been recorded recently. ... Kuwait has the seventh highest rate in the world.... [R]apid growth in early childhood increases the risk of diabetes, possibly by increasing the work-load on β-cells, and children grow considerably faster than they did a century ago. ... [A]n extremely rapid increase in the age-group under 5 years has been documented in some populations over the past 10-20 years. ...The hygiene hypothesis, initially developed to explain the parallel rise of asthma and allergy, argues

> that exposure to a range of infective agents in early childhood is necessary for successful maturation of the neonatal immune repertoire. In the absence of such exposure, a robust Th1 repertoire does not develop and potentially harmful Th2 patterns of response will persist in genetically susceptible individuals. Although this concept may prove unduly simplistic, lack of early stimulation could give rise to a failure of early immune regulation that might, according to genetic susceptibility, permit patterns of response predisposing to autoimmunity or allergy to develop at opposite ends of the Th1/Th2 spectrum. [citations omitted.]

C. Exhibit 2 is "Rapid Early Growth Associated with Type 1 Diabetes in European Children," pub. in 25 *Diabetes Care*: 1755-60 (2002) with the primary author Dr. C. Patterson, but submitted as a news item in www.medscape.com. It states:

> Results of a new population-based study confirm earlier reports that rapid growth in early childhood is a risk factor for type 1 diabetes among various European populations. ... The maximum difference between [patients with type 1 diabetes and controls] occurred between 1 and 2 years of age.... There was also a significant difference in excess standard deviation scores for BMI between patients and controls, which was seen 6 months after birth and peaked between 1 and 2 years of age....

C. Exhibit 3 is "Acidic Drinking Water May Increase Risk of Type 1 Diabetes," pub. in 25 *Diabetes Care* 1534-38 (2002) with the primary author Dr. L.C. Stene, but submitted as a news item in www.medscape.com. The authors state, "Low pH drinking water in individual households is strongly associated with the risk of type 1 diabetes...." The water was from wells in Norway. The odds ratio for the association was 2.3. P value was 0.002. Higher concentrations of zinc resulted in a decreased risk of diabetes. The mechanism may be related to the presence of microorganisms in the water at a particular pH level.

C. Exhibit 4 is "Congress examines childhood vaccine safety," by A. Dove pub. in 5 *Nature Medicine* 9: 970 (1999), but submitted from www.nature.com. Dr. Classen testified at this hearing, asserting that CDC had a conflict of interest because pharmaceutical companies exert undue

influence over it and the FDA. He testified that CDC data supports a causal association between hepatitis B vaccination and IDDM. The article continues, "Classen owns patents on several vaccine-testing protocols which would likely be required if legislators are persuaded to accept his interpretation of the study."

C. Exhibit 5 is "Responses to Media Stories–Response to Peter Jennings/World News Tonight (Oct. 5, 1998)" by S.L. Katz, pub. in National Network for Immunization Information as found in wysiwyg://35/http://www.immunizatio.../pressroom/media_response.cfm?ID=3. Dr. Samuel L. Katz, Co-Chair of the Vaccine Initiative, wrote a letter to Peter Jennings, anchor of ABC's World News Tonight because of a news report concerning vaccines causing diabetes type1, featuring Dr. Classen. Dr. Katz has been a pediatrician at Duke University for 40 years with experience in research, development, and policy regarding vaccines. The Vaccine Initiative's purpose is to provide to parents, health workers, legislators, and the media accurate, reliable information about vaccines, their benefits and risks, and the programs for their utilization in this country. Dr. Katz's co-chairman is Dr. Louis Sullivan, former secretary of HHS. Dr. Katz states about Dr. Classen:

> His theories are not new and have been reviewed at least three times in the past year by expert groups including diabetologists, immunologists, vaccinologists, geneticists, epidemiologists and biostatisticians all of whom have agreed unanimously that **Dr. Classen has totally misinterpreted data** that he has extracted from studies in Finland and elsewhere, and has **built a hypothesis for which there is absolutely no evidence**. These reviews have been sponsored by the Johns Hopkins University Institute for Vaccine Safety, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and the Vaccine Initiative of the Infectious Diseases Society of America and the Pediatric Infectious Disease Society. [emphasis added.]

C. Exhibit 6 is "Classen Immunotherapies, Inc. PR 09/11/00, describing Dr. Classen's opinion at http://www.vaccines.net/newpage18.htm Headed with the title, "Vaccines Proven To Be

Largest Cause of Insulin Dependent Diabetes in Children, Diabetics Advised to Seek Legal Counsel Now, Before Their Right to Compensation Expires," this is a publicity release from Dr. Classen in which he states that he provided data at the International Public Conference on Vaccination proving vaccines are the largest cause of IDDM in children, causing 80% of IDDM in children who receive multiple vaccines starting after two months of age. His data included DPT, MMR, hepatitis B, HiB, and other vaccines. "Lawyers attending the conference and who reviewed the data advise diabetics to seek legal counsel at once." Dr. Classen's publicity release goes on to state that his "research has been published in numerous journals and featured in national news reports."

C. Exhibit 7 is "Juvenile Diabetes and Vaccination: New Evidence for a Connection," pub. by National Vaccine Information Center, describing Dr. Classen's opinion, as found in https://www.909shot.com/Diseases/juvenilediabetes.html. The article discusses Dr. Classen's work. "Dr. Classen is developing ways to prevent autoimmune disease...." Id. at 3. The article goes on to discuss Dr. Classen's research and publications. It mentions that Dr. Classen's company "has developed pediatric immunization methods to prevent diabetes...." Id. at 4. The article describes Dr. Classen as a "reputable" researcher and notes he is not given government grants to do his research. Id. at 5. The National Vaccine Information Center accuses the government of having a conflict of interest in both monitoring vaccine safety and relying on data supplied by drug companies.

C. Exhibit 8 is "Do Infant Vaccines Cause Diabetes? Can You Sue if They Do. CDC and NIH Question Immunologist's Latest Claims," by D. Trecroci, as found in the December 2000 issue of http://www.diabetesinterview.com/archive/december/dec2-00.shtm. This is the article attached to the undersigned's Order of November 22, 2002, as Tab A, described supra.

On March 25, 2003, the undersigned filed a further exhibit in this case: C. Exhibit 9: "Special Article. Addressing Parents' Concerns: Do Vaccines Cause Allergic or Autoimmune Diseases?" by P.A. Offit and C.J. Hackett, 111 *Pediatrics* 3:653-59 (Mar. 2003). Offit and Hackett include a discussion of Dr. Classen's hypothesis that four doses of HiB in Finnish children resulted in a higher incidence of IDDM than one dose of HIB. Offit and Hackett state "the analytical methods used in [Classen's] Finnish study of Hib vaccine were incorrect, and there were no significant differences in the incidence of type 1 diabetes in Hib-vaccinated infants 10 years later. In addition, 21,421 children who received the Hib conjugate vaccine between 1988 and 1990 in the United States were followed for 10 years and the risk of type 1 diabetes was 0.78 when compared with a group of 22,557 children who did not receive the vaccine."[10] Id. at 7. Citing Black, DeStefano, Heijbel, Graves, and Hummel, the authors conclude that vaccinations do not increase the risk of IDDM.

The Centers for Disease Control has a website discussing and rejecting Dr. Classen's thesis that vaccines cause IDDM:

http://www.cdc.gov/nip/vacsafe/concerns/diabetes/q&a.htm

Diabetes and Vaccines

> At a glance: In 1998 a researcher presented a theory suggesting that vaccines, depending on when they are administered, may increase or decrease the risk that certain people may develop type 1 diabetes, previously called juvenile onset or insulin-dependent diabetes mellitus (IDDM). The cause of type 1 diabetes is not completely understood but it is believed that genetic and environmental factors may be involved. Vaccinations have been studied as a possible environmental risk factor and the scientific

[10] Citing to "Lack of association between receipt of conjugate haemophilus influenzae type B vaccine (HbOC) in infancy and risk of type 1 (juvenile onset) diabetes: long term follow-up of the HbOC efficacy trial cohort," by S.B. Black, et al., 21 *Pediatr Infect Dis J* 5:568-89 (June 2002).

studies conducted have found no relationship between immunizations and type 1 diabetes.

Questions answered on this page:

1. What is diabetes?
2. Do vaccines cause diabetes?
3. What about evidence that suggests vaccines cause diabetes?
4. What is being done to monitor the safety of vaccines?

1. What is diabetes?

Most of the food we eat is turned into glucose, or sugar, for our bodies to use for energy. The pancreas, an organ that lies near the stomach, makes a hormone called insulin to help glucose get into the cells of our bodies. If a person has diabetes, their body can't make enough insulin or can't use its own insulin as well as it should. This causes sugar to build up in the blood. Diabetes is classified into two main types:

Type 1 – Previously known as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. In Type 1 diabetes, which accounts for 5-10% of all diabetes cases, the body does not produce insulin. Risk factors are less well defined for type 1 diabetes than for type 2 diabetes, but genetic, environmental and autoimmune factors are involved in the development of this type of diabetes.
Type 2 – Previously known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes. In Type 2 diabetes, which accounts for 90-95% of all cases of diabetes, either the body does not produce enough insulin or the insulin does not work. Risk factors for type 2 diabetes include older age, obesity, family history, impaired glucose tolerance, physical inactivity and race/ethnicity (African Americans, Hispanic/Latino Americans, Native Americans, and some Asian Americans and Pacific Islanders are at increased risk).

In discussion below, "diabetes" refers to type 1.

For more information about diabetes, see the Centers for Disease Control and Prevention's diabetes program website at http://www.cdc.gov/diabetes/

2.Do vaccines cause diabetes?

No. Carefully performed scientific studies show that vaccines do not cause diabetes or increase a person's risk of developing diabetes (DeStefano 2001, EURODIAB Substudy 2 Study Group 2000, Karvonen 1999, Heijbel 1997, Parent 1997, Dahlquist 1995, Hyoty 1993, Blom 1991). In 2002, the Institute of Medicine reviewed the existing studies and released a report concluding that the scientific evidence favors rejection of the theory that immunizations cause diabetes. Furthermore, DeStefano and colleagues (2001) recently conducted the first study looking at whether the timing of childhood vaccinations, particularly of Hepatitis B, is related to the risk of a child getting diabetes. This study, which examined data from 1,020 children in the U.S., did not show an association between any of the recommended childhood vaccines and diabetes, regardless of when the vaccines were given. Other studies also provide evidence that vaccination does not cause diabetes:

A European study that examined 900 diabetic and 2,302 non-diabetic children found a slight relationship between infections during early infancy and risk of developing diabetes. However, the researchers did not find a relationship between any of the common childhood infections or childhood vaccines and diabetes in children. (EURODIAB Substudy 2 Study Group 2000)

A study conducted in Sweden looked at 1,267 diabetic children in two groups: a group of children that were born during the time that pertussis vaccination was used and a group of children that were born after pertussis vaccine had been removed from the immunization schedule. The researchers found no difference in the incidence rate of diabetes between the children born before and the children born after 1979, when pertussis was excluded from routine immunizations in Sweden. (Heijbel 1997)

The results from a study that examined 339 diabetic and 528 non-diabetic Swedish children showed that children that received measles vaccine were slightly protected against getting diabetes. The study showed no relationship, positive or negative, between tuberculosis, smallpox, tetanus, whooping cough, rubella and mumps vaccines and diabetes in children. (Blom 1991)

3. What about evidence that suggests that vaccines cause diabetes?

The only evidence suggesting a relationship between vaccination and diabetes comes from Dr. John B. Classen (Classen 1996; Classen and Classen 1997; Classen and Classen 2002). He has suggested that certain vaccines if given at birth may decrease the occurrence of diabetes, whereas if initial vaccination is performed after 2 months of age the occurrence of diabetes increases. Dr. Classen's studies have a number of limitations and have not been verified by other researchers.

> This theory is based on results from experiments in laboratory animals, as well as comparisons of the rates of diabetes between countries with different immunization schedules (Classen, 1996; Classen & Classen 1997). Applying findings from laboratory animals to humans is fraught with uncertainty. Findings that are noted in animals cannot be directly applied to people because of the large biological differences. In addition, many of the animal experiments involved anthrax vaccine, which is not used in infants and children.
> Comparison of diabetes rates between countries provides weak evidence because many factors, including vaccination schedules, may differ by country. For instance, comparisons between countries included vaccines that are infrequently used in the U.S. (BCG) or are no longer used (smallpox). Furthermore, factors such as genetic predisposition and a number of possible environmental exposures unrelated to vaccines, may influence the development of diabetes in different countries.

Dr. Classen also performed an analysis of data from a large study conducted in Finland of Haemophilus influenzae type B (Hib) vaccine. Over 100,000 children were randomly assigned to receive either 4 doses of vaccine starting at 3 months of age or a single dose at 24 months. Over about a 10-year follow up period, 205 children in the multiple dose group developed diabetes compared with 185 in the single dose group.

> These results are inconclusive because the exact number of children in each group is not known and the noted

differences may not be statistically significant (that is, they could be due to "chance").
The results from a similar study using the same data from Finland were not the same as Dr. Classen's results (Karvonen et al. 1999). This study was similar to Dr. Classen's study except that it compared children in 3 (rather than 2) different groups: 1) children that were born before Hib vaccination was recommended (and therefore did not receive the shot as part of their routine immunizations), 2) children that began receiving Hib vaccine at 3 months of age, and 3) children that received a single dose of Hib at 24 months. This study did not find a difference in diabetes risk between any of the 3 groups of children.

Dr. Classen recently performed another analysis using the same data from the group of children in Finland (Classen and Classen 2002). In this study Dr. Classen suggests that by the age of 7 years old a greater number of diabetes cases occurred in Finnish children that had received the Hib vaccine than in children that had not received the vaccine.

In order for an association between Hib vaccination and diabetes to be confirmed, the results would have to be replicated in several other scientific studies. No other studies, not even one using the exact same data from the children in Finland (Karvonen 1999), have found a relationship between Hib vaccine and an increase in diabetes (DeStefano 2001, EURODIAB Substudy 2 Study Group 2000).
It appears that Dr. Classen may have conducted his statistical analysis after seeing the results and noting that the largest difference was apparent by 7 years. The validity of this type of 'post-hoc' statistical testing, however, is highly questionable. When the full 10 years of follow-up was evaluated the differences were not statistically significant, which is also what was found by Karvonen and colleagues.

4. What is being done to monitor the safety of vaccines?

To assure the safety of vaccines, The Centers for Disease Control and Prevention (CDC), the Food and Drug Administration

(FDA), the National Institutes of Health (NIH), and other Federal agencies routinely monitor vaccine safety and conduct research to examine any new evidence that would suggest possible problems with the safety of vaccines. The CDC's Vaccine Safety Datalink (VSD) project links the immunization and medical records on members of seven HMOs, totaling 2.5% of the US population for various vaccine safety studies. The VSD project is a powerful and cost-effective tool for the on-going evaluation of vaccine safety. The Vaccine Adverse Event Reporting System, or VAERS, was designed to give health care workers and others a place to report possible problems following vaccination. VAERS helps the FDA and CDC to continuously monitor vaccine safety. To request a VAERS form or to get more information about VAERS, please call 1-800-822-7967 or go to the VAERS website http://www.vaers.org.

Or, visit the CDC's National Immunization Program's web site: http://www.cdc.gov/nip

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DISCUSSION

Because IDDM is not a Table injury, petitioner must prove causation in fact. To satisfy her burden of proving causation in fact, petitioner must offer "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury. A reputable medical or scientific explanation must support this logical sequence of cause and effect." Grant v. Secretary, HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Agarwsal v. Secretary, HHS, 33 Fed. Cl. 482, 487 (1995); see also Knudsen v. Secretary, HHS, 35 F.3d 543, 548 (Fed. Cir. 1994); Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993).

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

association is not sufficient to prove causation in fact. Hasler v. US, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984).

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

In reaching her decision, the undersigned relies upon the United States Supreme Court's decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 US 579 (1993). The Supreme Court stated that the first criterion for accepting scientific evidence is that the expert's testimony pertaining to scientific knowledge be not only relevant, but also reliable. Secondly, the "scientific" aspect of the testimony must be grounded in the methods and procedures of science. Thirdly, the "knowledge" aspect of the testimony must rely on more than subjective belief or unsupported speculation. Id. at 590.

The Supreme Court further stated:

> [I]n 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.

Id.

Daubert focuses on evidentiary reliability. The Supreme Court stated: "In a case involving scientific evidence, *evidentiary reliability* will be based upon *scientific validity*." Id. at n.9 (emphasis included). The expert's opinion should have a "reliable basis in the knowledge and experience of his discipline." Id. at 592.

The Supreme Court instructed trial courts to assess preliminarily whether the reasoning or methodology underlying the expert's testimony is scientifically valid as well as "whether that reasoning or methodology properly can be applied to the facts in issue." Id. at 593.

A key consideration in assessing the scientific reliability of testimony is whether the theory at issue can be or has been tested. Id. Another consideration is whether the theory proffered has been accepted after peer review and in publications. Although not essential to establish reliability, peer review, i.e., the scrutiny of the scientific community, represents "good science" because it detects more likely substantive flaws in methodology. Id.

Further, when a particular scientific technique is at issue, the court should ordinarily consider the known or potential rate of error and the standards controlling the technique's operations. Id. at 594. The Supreme Court stated that a trial court may be properly skeptical about a known technique the scientific community only minimally supports. Id. "The focus ... [of the trial court] must be solely on principles and methodology, not on the conclusions that they generate." Id. at 595.

The Supreme Court, recognizing the difference between the quest for truth in the courtroom and the quest for truth in the laboratory, emphasized that scientific inquiry advances "by broad and wide-ranging consideration of a multitude of hypotheses," whereas the trial court is not intent on "the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes." Id. at 597.

In conclusion, Daubert stands for the principle that a trial judge's task is to ensure that an expert's testimony both rests on a reliable foundation and is relevant to the issues of the case. "Pertinent evidence based on scientifically valid principles will satisfy those demands." Id.

Here, we have overwhelming evidence in epidemiologic and medical articles, based on extensive research in various countries, concluding that there is no valid proof that childhood vaccinations cause IDDM.[11] Dr. Classen[12] stands alone (with his first cousin on occasion) in his credo that 50% of IDDM in children under the age of seven years is caused by vaccinations.[13] He analyzed the Finnish data in a manner so as to come to the exact opposite conclusion of the Finnish epidemiologists who analyzed the same data.

Evidence shows that every year, all over the world, the incidence of IDDM increases. No one knows why IDDM has increased over the years all over the world. Dr. Halsey stated that Dr. Classen left out points of comparison in comparing the four-dose group with the unimmunized that

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[11] Literature and other material totally opposes Dr. Classen's thesis, even specifically discussing it: DeStefano (P. Exs. 78 and 95), EURODIAB Study (P. Ex. 79), Graves (P. Ex. 80), the IOM (P. Ex. 83), Hiltunen (P. Ex. 86), Rami (P. Ex. 87), Heijbel (P. Ex. 88), the Institute for Vaccine Safety Workshop (P. Ex. 97), Jefferson (P. Ex. 99, R. Ex. H-9), Petousis-Harris (R. Ex. H-10), Hummel (R. Ex. I-9), Halsey (R. Ex. U), Tuomilehto (R. Ex. W), and the CDC website.

[12] It is doubtful that Dr. Classen fulfills the American Medical Association (AMA) guidelines for expert witnesses: H.265-994 Expert Witness Testimony: (3)(a) "Existing policy regarding the competency of expert witnesses ... (BOT Rep. SS A-89) is reaffirmed, as follows: The AMA believes that the minimum statutory requirements for qualification as an expert witness should reflect the following: (i) that the witness be required to have comparable education, training, and occupational experience in the same field as the defendant; (ii) that the occupational experience include active medical practice or teaching experience in the same field as the defendant; and (iii) that the active medical practice or teaching experience must have been within five years of the date of the occurrence giving rise to the claim." www.ama-assn.org. Dr. Classen does not have education, training or occupational experience in the fields of epidemiology and immunology comparable to respondent's experts. In addition, his active medical practice consists of walk-in clinic activities, such as sewing lacerations, an area totally unrelated to his testimony. He has neither active medical practice nor teaching experience in epidemiology and/or immunology within 5 years of the date of Jonathan's development of diabetes.

[13] Occasionally, Dr. Classen testified that 51% was the figure, presumably to create a more likely than not conclusion. His figures, whether 50% or 51%, are suspect because his methodology is rejected by every scientist and doctor who has analyzed it, except for his cousin.

would have shown a lack of statistical significance. Dr. Classen took only the data (using the wrong analytic method) that would produce the clusters he wanted. He defended his ending his analysis at 7 years, rather than at the 10-year point that Dr. Tuomilehto did because Dr. Classen proclaimed (with three exclamation points in his letter responding to Dr. Tuomilehto's letter) that the point of doing the study was to produce statistical significance. In other words, his version of doing science is to have a goal and manipulate the figures to achieve that goal.

Dr. Classen complained that Dr. Tuomilehto compared only the one-dose group (vaccinated at 2 years of age) with the unimmunized, but not the four-dose group (vaccinated at ages 3, 4, 6 and 14 to 18 months) with the unimmunized. But Dr. Tuomilehto did compare the four-dose group with the one-dose group and found no difference in the risk of IDDM. The relative risks for the one-dose group compared to the unimmunized and the four-dose group compared to the one-dose group were near 1.0. Since the one-dose and four-dose groups had no significant difference in the risk of IDDM, it makes no difference if Dr. Tuomilehto compared only the one-dose group to the unimmunized since the relative risk was the same. Dr. Tuomilehto concluded that both HiB vaccine and the timing of its administration were unrelated to the incidence of IDDM.

Dr. Classen's stance against the entire medical establishment (or, as he terms it, "the biggest people") does not add to, but rather detracts from, his credibility. His testimony that science does not operate by consensus is self-serving since the consensus opposes his conclusions. Legally, the undersigned is compelled to find that someone who defies scientific methods acceptable to those trained in the field of epidemiology lacks the trustworthiness and reliability that the United States Supreme Court states is the sine qua non for accepting medical and scientific testimony. That others who are trained (whereas Dr. Classen is not) in the fields of epidemiology, immunology, and

endocrinology do not know the cause of childhood IDDM does not make Dr. Classen right because he is certain and them wrong because they are uncertain about the cause. Certitude based on unreliable methods is worthless.

Dr. Classen's unreliable methods and analysis include: multiplying the odds ratios or relative risks of various vaccines to obtain a cumulative incidence of IDDM; using a one-tailed instead of a two-tailed test in the Finnish study; changing the axes from Dr. Tuomilehto's fax which changed the curves for the Finnish data; doing a meta-analysis of different vaccines; selectively picking data points from the Finnish and New Zealand data that agree with his hypothesis while eliminating those that do not; and ignoring the other environmental factors that can affect incidence of IDDM (year of birth, latitude, Caesarean section, older maternal age, infections, day care, breast feeding, growth rate in infancy, water acidity, and the linear rise in IDDM rates even before vaccinations were instituted) because calculating risk of IDDM from them would be difficult. He commits, as Dr. Halsey says, the ecological fallacy, emphasizing one intervention (vaccination) while ignoring all other environmental interventions.

To reach the opposite conclusion, that Dr. Classen's methodology and conclusions are correct and all the credentialed, experienced epidemiologists who have criticized him internationally are wrong, would be to posit a world-wide conspiracy to sicken children or to have an interest in making certain that the cause of their illness remains unknown. This would be a ludicrous conclusion.

The United States Supreme Court in Kumho Tire Co. v. Carmichael, 526 US 137, 141 (1999), stated that "scientific expert testimony... is admissible only if it is both relevant and reliable." This is important in order "to make certain 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." Id. at 152.

Intellectual rigor is missing from Dr. Classen's testimony, papers, experience, and training, not to mention that he does not practice in the relevant field. He earns a living by taking care of emergency patients. His supposed training in immunology at NIH was minimal according to his former supervisor, an outstanding immunologist (Dr. Shevach). Dr. Classen is not board-certified in anything, much less epidemiology or immunology. He obtained patents dealing with vaccination schedules and incorporated in order to reap profits should any court rule that the current vaccination schedule leads to IDDM.

Dr. Classen posits to this court that the court need not regard statistical significance as meaningful since the articles he describes show a trend that he says is sufficient to prove causation. But the undersigned relies upon those knowledgeable in the field and what is persuasive to them in order to evaluate the credibility of a conclusion as to causation. Epidemiologists do not make causal associations in the absence of statistical significance.

In Haim v. Secretary of HHS, No. 90-1031V, 1993 WL 346392 (Fed. Cl. Spec. Mstr. Aug. 27, 1993), a case before the undersigned, in which the expert there also testified that statistical significance was not important in finding a causal relationship, the undersigned rejected his testimony, id. at *11, emphasizing that reliability of data is vital in finding an opinion credible. In reaching her decision, the undersigned relied upon Daubert.

We know that various countries, including Finland and Sardinia, have incidences of IDDM that far exceed that of other countries, with Finland's rate of IDDM being the highest in the world. Shall the undersigned conclude that Finnish and Sardinian children receive more vaccinations (after

the age of two months) than anyone else in the world? Dr. Classen does not explain this phenomenon. If childhood vaccines cause IDDM, then wherever children receive vaccinations, there should be a uniform rate of IDDM two to four years later. But that does not happen.

We know from the literature that different ethnic groups have much higher rates of IDDM than others do. We know that different countries in different climates at different seasons have higher rates of IDDM depending on the latitude, climate, and season. The acidity of water and the growth rate of infants affect their risk of developing IDDM. These are all environmental factors. In the one article that Dr. David Carey Classen co-authored with Dr. John Bartholew Classen which Dr. David Classen includes in his CV, the authors state there are numerous factors that can cause IDDM, including advanced maternal age at pregnancy, child daycare, infections, etc. Jonathan had at least five of them: living in New York (a northern climate), a birth mother of nearly 38 (advanced maternal age), Caesarean birth, foster care for three months, and who knows how many infections. Which of these factors shall the undersigned conclude is substantial? Are all of them, including vaccination, substantial? Dr. Classen focuses on only one factor (vaccination) and excludes all others.

Focusing solely on vaccinations, as Dr. Classen does, to say that in the life of an individual, such as Jonathan Baker, his childhood vaccines caused his IDDM is dishonest. If Dr. Classen were being honest, he would state that, although he firmly believes that childhood vaccines administered after the age of two months cause IDDM in 50% of the cases, he does not know if Jonathan Baker falls within the 50% that vaccines cause or the 50% that environmental factors other than vaccines cause. By intermittently switching the number to 51%, Dr. Classen saves himself the trouble of

figuring out in which group Jonathan belongs. But the undersigned does not accept Dr. Classen's opinion.

Dr. Classen's explanation of his 50% figure attributing causation to vaccines is also suspect because it depends on HiB's causing 25% of IDDM from his analysis of the Finnish data. Then he loads onto that 25% figure the risk from other vaccines by multiplying odds ratios and relatives risks from them. (The undersigned noticed during the two-day hearing that Dr. Classen frequently said odds ratio when he meant relative risk and vice versa. He views them as identical.) Arriving at the incidence of risk of IDDM by multiplying odds ratios and/or relative risks from other vaccines is not done, according to Dr. Halsey.

Dr. Classen does not give percentages of causality to maternal age, viruses, ethnic group, Caesarean birth, day care, consumption of milk, acidity of water, rate of infant growth, etc. because he stated that would be too difficult to do. But difficulty does not justify ignoring these other factors. Even though the randomization of the Finnish vaccinees into birth on even and odd days would take care of these other factors, for the purposes of comparing them to each other, they do not affect the role of other environmental conditions on the unvaccinated, historical group, a point Dr. Tuomilehto made in his article as a caveat for his own comparison of the one-dose group with the unvaccinated, historical controls.

Even though Dr. Classen is strongly motivated by financial interests to show a causal connection between vaccinations and IDDM, his own Figure 2 in Exhibit 55, page 39, depicting the rate of IDDM in the United Kingdom when DPT administration was increased or decreased shows exactly the opposite results compared to his testimony. Figure 2 shows that, when DPT administration decreased, two to four years later, the rate of IDDM increased rather than decreased.

And when the rate of DPT vaccination increased, IDDM decreased four years later. When the undersigned questioned Dr. Classen about the results of his Figure 2 because they contradicted his testimony, he responded that he would not expect the Court to agree with every paper he published. This is not an honest response. It is not a question of disagreeing with his papers, but of his papers being consistent with his own conclusions. Consistency was one of Sir Bradford-Hill's nine criteria of causation, yet Dr. Classen's testimony is inconsistent with his own work.[14] Dr. Shevach, in the Diabetes Interview article, stated that Dr. Classen does not know what he is talking about. Dr. Zweiman testified that no respected immunologist agrees with Dr. Classen's conclusions. Dr. Bercu, a pediatric endocrinologist, testified that no one knows the cause of IDDM.

Dr. Classen's inappropriate methodology, profit motive, sole focus on vaccines to the exclusion of other environmental factors, and absence of epidemiological training, board-certification, and relevant professional experience make his testimony unpersuasive and not credible. When comparing him to Dr. Halsey and Dr. Tuomilehto, two giants in the field of epidemiology whose accomplishments and achievements are extraordinary, the undersigned can only marvel at the lack of training and expertise of Dr. Classen, and be appalled at his flaunting of sound analytical methods.

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[14] Petitioner submitted the nine Bradford-Hill criteria in her Exhibit 71: "Causal Association in Pharmacovigilance and Pharmacoepidemiology. Thoughts on the Application of the Austin Bradford-Hill Criteria," by S.A.W. Shakir and D. Layton, 25 *Drug Safety* 6:467-71 (2002). They state, at 468, "In epidemiology, a relative risk of less than two is considered to indicate a weak association." Since Dr. Classen was touting relative risks and odds ratios of just over one, his work would not satisfy the first Bradford-Hill criterion of strength of association.

Petitioner has failed to prove a prima facie case that, more likely than not, childhood immunizations were a substantial factor in causing Jonathan's IDDM and but for his receipt of these vaccinations, he would not have had IDDM.

CONCLUSION

Petitioner's petition is dismissed with prejudice. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court is directed to enter judgment in accordance herewith.

IT IS SO ORDERED.

_____ _____

DATE Laura D. Millman
Special Master