Respondent's Exhibit T

Medical Expert Report for Cedillo v. Sec'y HHS, No. 98-916V.

Report by Michael D. Gershon, M.D., Professor of Pathology and Cell Biology, Columbia University, College of Physicians and Surgeons.

Date of Report: 4/24/07

Qualifications

I am a neurogastroenterologist. I obtained my M.D. degree from Cornell University in 1963 with prizes for the highest academic record and for undergraduate research. My research training, however, began earlier, when I took a year's leave for this purpose while still a medical student. Work accomplished during that year resulted in my first peer-reviewed publication (Gershon and Ross, 1962). That publication concerned serotonin-producing cells in the gut and their relationship to a severe immunological reaction called anaphylactic shock. I have been interested in immunology, the bowel, and its disorders ever since. I received postdoctoral training in Anatomy at Cornell and in Pharmacology at Oxford. I was appointed an Assistant Professor at Cornell in 1966, Associate Professor in 1969, and Professor in 1975. Later that year, I moved to Columbia University College of Physicians and Surgeons as Professor and Chair of the Department of Anatomy & Cell Biology. I stepped down as Chair in July of 2006, although I have retained my Professorial appointment, my research program, and teaching. The Department of Anatomy & Cell Biology was fused with the Department of Pathology to create a new Department of Pathology & Cell Biology. I am now a Professor within that Department.

Since my original publication in 1962, I have authored over 300 scientific articles and chapters and I have written a highly successful and well-reviewed book on the function of the bowel for the general public, entitled "The Second Brain" (Gershon, 1998). I have been elected president of the Cajal Club (Research society of Neuroscientists), the American Association of Anatomy, Cell Biology, and Neurobiology Chairs, and the American Association of Anatomists. I have been awarded the Tousimis Prize by the American Association of Anatomy Chairmen and I have won the Henry Grey Award of the American Association of Anatomists (its highest honor). Other honors have included the Camillio Golgi and François I medals from, respectively, the Fidia Foundation and the Collège de France, at which I was, in addition, an honored visiting professor. I have also been elected a Fellow of the American Association for the Advancement of Science. I have served on the editorial boards of many scientific journals, including at present, *Gastroenterology*. I have served on a number of initial review groups (Study Sections) to evaluate research for the National Institutes of Health and have recently agreed to serve again for a full term as a regular member of the Clinical and Integrative Gastrointestinal Pathobiology (CIGP) Study Section. I have also served on the advisory panel of the Food and Drug Administration on Gastrointestinal Drugs and have reviewed research grant proposals as a member of study section of the March of Dimes. I also serve on the Scientific Advisory Board of Cure Autism Now, which recently merged with Autism Speaks.

My research has been supported continuously since 1967 by individual peer-reviewed research grants from the National Institutes of Health as well as by grants from private foundations and industry. Because of my early work and pioneering discoveries,

I have been called the "father of Neurogastroenterology"[*]. These seminal discoveries underlie current understanding of the function and development of the enteric nervous system ("the second brain"), serotonin signaling in the gut, and the rationale for treating gastrointestinal disorders with drugs that affect serotonin signaling. Most recently, I have helped to determine how varicella zoster virus infects cells, spreads to new hosts, and how, unexpectedly, it infects and becomes latent in enteric neurons (the intrinsic nerve cells of the bowel).

I have provided testimony regarding whether vaccination against measles, mumps, and rubella (MMR) causes autism for committees of the Institute of Medicine (Halsey and Hyman, 2001) and the United States House of Representatives[*]. My analysis of this subject was featured in an exhibit by the Science Museum (Exhibition Road, London, UK), entitled "The MMR Files".

By virtue of my knowledge and experience, as described above, I feel qualified to render an expert opinion to the Court.

Basis of Opinions

All of my opinions are my best evaluations of medical and scientific evidence. They are based on my education, training, research, and review of the literature. I have reviewed the information about this case and my opinions are evidence-based and expressed to a reasonable degree of medical and scientific probability.

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[*] see, http://www.google.com/search?client=safari&rls=en&q=father+of+neurogastroenterology&ie=UTF-8&oe=UTF-8

[**] Gershon, M.D. House of Representatives, Committee on Government Reform. 107th Cong. 1st Session (2001) Serial No. 107-29: 74-77, 178-89.

The Case

Others have summarized the case report on Michelle Cedillo. I will therefore recapitulate only some important elements, particularly those that relate to the petitioners' supposition that her MMR vaccination was causally related to her subsequent diagnosis of autism.

The prior history of Theresa Cedillo is notable for allergy, asthma, carpal tunnel syndrome, and high blood pressure prior to delivery, which necessitated induction of labor. Michelle was delivered with vacuum assistance and appeared to be normal at birth despite having an umbilical cord that was wrapped around her neck. On 9/7/94, Michelle was noted to be "gassy" and to have developed "colic". On 12/14/94, a rash was described on Michelle's stomach, which on 12/15/94 extended as "red spots" over her eyes and a rash on her torso. On 4/25/95, her head circumference was reported to be large (greater than in the 95th percentile), which is consistent with autism.

According to the mother's narrative, which was written after Michelle was diagnosed with autism, Michelle developed a 104.5°-105° F fever on 12/27/95 – seven days after her 12/20/95 MMR vaccination. The fever appeared to respond temporarily to Tylenol, but spiked the following day and was again reduced with Tylenol. On 12/30/95, a rash appeared and the fever broke, dropping to 101° F, and became normal on the following day. On 1/6/96, a second episode of fever occurred, accompanied by nasal discharge and gagging to the point of vomiting. On 3/15/96, Michelle was noted to have had a rash for 2.5 weeks on her face and neck.

In retrospect, symptoms consistent with ASD became apparent to Michelle's parents who focused their attention on the MMR vaccination and the febrile episode that followed it 7 days later. As is true of many children with ASD, a regression appears to occur around the second year of life, when a deficiency in language and socialization becomes striking in comparison to typical children of the same age. MMR vaccination is administered at this time, and it is natural for parents to attribute the autism to the vaccine. This attribution may be strong enough to motivate them to disregard reports, such as those of the American Academy of Pediatrics (Halsey and Hyman, 2001) and the Institute of Medicine*, that find no credible evidence in favor of the idea that MMR is a precipitating event in the development of autism. Moreover, most parents are, understandably, not able to appreciate the strong epidemiological evidence that refutes an association between MMR vaccination and autism (Chen et al., 2004; Dales et al., 2001; Fombonne et al., 2006; Honda et al., 2005; Madsen et al., 2002; Mangel and Koegel, 1984; Smeeth et al., 2004).

In Michelle's case, the diagnosis of autism appears to have been made on 7/21/97, which is 19 months after the MMR vaccination in question, by Karlsson Roth, Ph.D., a developmental psychologist. At the time of diagnosis, Ms. Cedillo's focus had narrowed to the febrile episodes following Michelle's 12/20/95 MMR vaccination. No vigorous examination of Michelle's medical history prior to MMR administration was undertaken to determine whether signs of autism appeared prior to that event (constipation and rash, both of which are features of subsequent morbidity, were described in her record prior to

* Institute of Medicine. Immunization and Safety Review: Vaccines and Autism. Washington, DC. National Academies Press: 2004.

MMR vaccination). Nevertheless, Dr. Roth did not attribute Michelle's autism to vaccination.

Theresa Cedillo provided inconsistent medical histories describing Michelle's symptoms in the period after MMR vaccination. If we assume, however, that a high fever did begin 7 days after her MMR vaccination, it would not necessarily be unexpected. A high fever of this kind is reported in about 6% of children receiving MMR vaccine for the first time (LeBaron et al., 2006). The median onset is 5-10 days post-vaccination and the duration is 2-5 days; no treatment is usually necessary.

No attempt was made to ascertain whether this febrile episode was related to any exposure other than vaccination. Of particular note, the pattern of symptoms – fever and the subsequent appearance of a rash as a harbinger of the fever breaking – is consistent with infection with HHV-6B (roseola), a relatively common childhood illness. Regardless, a fever following MMR vaccination is not an unanticipated or adverse event. Additionally, there is no reason to associate the MMR vaccination with the febrile episode that occurred over two weeks after vaccination. That illness occurred a week after the first fever resolved, and was accompanied by symptoms suggestive of an upper respiratory illness, including stuffy nose, nasal discharge, and gagging to the point of vomiting. The differential diagnosis was sinusitis v. flu, and her physician treated it, evidently successfully, with antibiotics.

Michelle has a long gastrointestinal history that includes constipation to the point of fecal impaction, necessitating medical clearance (for example on 8/14/00, 12/21/01, and 1/17/02), diarrhea, eosinophilic esophagitis/gastritis, and gastroesophageal reflux

disease (GERD). The latter was diagnosed as part of the Repligen secretin study, the protocol of which required a formal gastroenterological evaluation. The diarrhea may have been overflow because constipation seems to have been Michelle's most vexing problem. Michelle's gastrointestinal complaints have led to upper, lower, and capsule endoscopies. Erosive esophagitis was detected on upper endoscopy and biopsies revealed eosinophilic infiltrates, which were consistent with the diagnosis of GERD. The eosinophils were not explained; however, these cells are not characteristic of immune responses to viral infection and are not suggestive of a measles infection of the bowel. Eosinophilic esophagitis is thought to be associated with a local hypersensitivity to food or inhaled antigens (Lucendo et al., 2007). It is thus in keeping with Michelle's history of allergy and the genetic history of allergy in her mother.

Erosions of the esophagus in GERD are usually attributed to the reflux of gastric acid. This is likely to have been the case for Michelle, although erosions can occur in eosinophilic esophagitis. In Michelle's case, the esophagitis was treated with a proton pump inhibitor to prevent the secretion of acid and the esophagitis resolved, suggesting that the erosions were due to acid reflux. Reflux in turn occurs for a number of reasons, such as inadequate gastric compliance, delayed gastric emptying, hiatus hernia, or abnormal relaxation of the lower esophageal sphincter, none of which include measles infection. There is no reason to associate GERD, which is highly common in America, even in children, with MMR or with measles. In fact, the "incidences of presentation for GERD, abdominal pain of unknown origin, and constipation are among the highest for pediatric disorders, and a cause for repeated medical consultations" (Chitkara et al.,

2007). Symptoms analogous to Michelle's are thus extremely widespread among typical children, as well as those with autism.

Lymphonodularity of the distal esophagus, duodenal bulb, terminal ileum, and sigmoid colon were noted as a result of upper and lower endoscopies conducted in January of 2002. These findings are not dissimilar to those in a small series of patients with autism and gastrointestinal complaints reported in the *Lancet* in 1998 (Wakefield et al., 1998), which later were proposed to represent "autistic enterocolitis" (Wakefield, 2002; Wakefield and Montgomery, 2000). These findings were said to be associated with a new variant of "regressive autism", although many autistic children lose skills that they once acquired, giving the appearance of regression. The idea that there is a new variant of "regressive autism" has been challenged and, in any case, it is not unique to a particular set of patients who become autistic following vaccination against MMR (Fombonne and Chakrabarti, 2001). Lymphonodularity is itself a non-specific finding and is seen so often during endoscopies (Franken, 1970; Riddlesberger and Lebenthal, 1980; Rossi, 1988), especially in the ileum (Kokkonen and Karttunen, 2002), of children who are not autistic, that it cannot be taken as diagnostic of an inflammatory bowel disease (IBD) (Shaoul et al., 2006) or a purported subset of IBD described by Wakefield and associates as "ASD-GI" or "autistic enterocolitis." It should be noted in this regard that ten of the co-authors of Wakefield's 1998 *Lancet* paper that introduced the concept of "ASD-GI" or "autistic enterocolitis" retracted the essentials of its conclusions (Murch et al., 2004).

Samples of intestinal mucosal biopsies from Michelle's terminal ileum were sent to the laboratory of Dr. John O'Leary in Dublin, Ireland, for "measles virus analysis".

TaqMan Polymerase Chain Reaction (PCR) in this laboratory is reported to have confirmed the presence of RNA encoding components of measles virus RNA in the biopsy specimen. It is important to consider the possible significance of this observation. As mentioned above, the epidemiological evidence refuting any link between MMR vaccination and autism is strong and has been strengthened by the repetitive agreement of many large studies conducted in North America, Europe, and Asia (Chen et al., 2004; Dales et al., 2001; Fombonne et al., 2006; Honda et al., 2005; Madsen et al., 2002; Mangel and Koegel, 1984; Smeeth et al., 2004). In fact, as will be discussed below, the detection of RNA encoding components of measles virus by TaqMan PCR by the methods used in the laboratory of Dr. John O'Leary cannot be taken to mean that replicating measles virus actually exists in the tissues sent for assay.

PCR studies that have the appearance of supporting the idea that measles virus from MMR vaccination chronically infects the bowel (Martin et al., 2002; Uhlmann et al., 2002) or peripheral blood mononuclear cells (lymphocytes and monocytes) (Kawashima et al., 2000) have been published. Sequence data was not reported in the GI studies (Martin et al., 2002; Uhlmann et al., 2002), but in the peripheral blood mononuclear cells, sequencing was said to implicate the vaccine virus in the majority of samples (Kawashima et al., 2000).

The validity of PCR-based assays is entirely dependent on the primers used. The degree of amplification is tremendous; therefore, false positive PCR products are always a possibility and have to be rigorously ruled out. Concerns have been raised about the methods used to detect RNA encoding components of measles virus (Afzal and Minor, 2002); however, these concerns are as nothing compared to recent data that indicates that

inappropriate primers were utilized by the groups who thought they had detected RNA encoding components of measles virus in gut and peripheral blood mononuclear cells (D'Souza et al., 2006). Upon careful evaluation of the products of PCR amplification – with size, melting point, and complete sequencing – the D'Souza et al. authors state: "No sample from either autism spectrum disorder or control groups was found to contain nucleic acids from any measles virus gene." Further, "there was no difference in anti-measles antibody titers between autism and control groups." These observations led to the conclusions that the PCR data published in support of the linkage of MMR to autism is unlikely to be valid. In contrast, the refutation of the claim that RNA encoding components of measles virus can be detected in patients who have been given MMR vaccine can be taken as reliable because it has been independently replicated in another study by an experienced and highly regarded group (Afzal et al., 2006).

The addition of the new evidence against the persistence of measles virus in children with autism spectrum disorders to the overwhelming epidemiological evidence that MMR vaccination is not linked to autism has caused the purported association to be denigrated as an "urban legend … an apocryphal story often told in the form of a cautionary tale that is related or transmitted as if true … however, careful examination of the legend's origin and its content ultimately reveals it to be false and without basis." (Shevell and Fombonne, 2006) An editorial in *Pediatrics* (Katz, 2006) commenting on the molecular evidence has said of the new reports: "Hopefully, the reliable results from these 2 laboratories will convince those who retain the belief that MMR vaccination causes ASDs and/or inflammatory bowel disease that this hypothesis in no longer tenable."

Michelle's biopsies were sent to the laboratory that utilized primers that have been demonstrated not to work and to yield false-positive claims of detection of persistent "measles virus" in the gut. In fact, it was stated by Dr. Oldstone, who is repeatedly referenced in Dr. Kinsbourne's report, that the O'Leary laboratory's "record of performance would not be acceptable for certifying a clinical laboratory"[*]. The positive finding of RNA encoding components of measles virus in Michelle's biopsies, therefore, cannot be taken to mean that this RNA is actually present in her bowel.

Even if RNA encoding components of measles virus had been present in the gut, the amplification of a nucleic acid is not the same thing as culturing the virus. To show persistent infection, one should recover the virus. No one has ever been able to recover measles virus from the gut of a patient to whom MMR vaccine has been given and certainly no one has ever done so from the supposedly infected lymphoid cells in the bowel or elsewhere in patients with autism. RNA is usually thought of as unstable and transient; however measles virus is an RNA virus. Cells archive their genetic information in DNA and transcribe messages that are carried to the cytoplasmic protein synthetic machinery by species of RNA to be translated into protein. The messenger RNAs are discarded and made again when needed, while the archival DNA is stable. Measles virus, however, archives its genetic information in RNA, which is more stable than a typical messenger RNA, and which may be made more stable by binding to protein. Even messenger RNAs can, under appropriate conditions, be long-lasting. Persistence of measles virus RNA in tissues without replicating virus is thus conceivable and may occur

[*] Oldstone, M.B.A. House of Representatives, Committee on Government Reform. 107th Cong. 1st Sess. (2001). Serial No. 107-29: 193-194.

in immune cells, which are specialized to hold onto fragments of macromolecules. Amounts of persisting nucleic acid would likely be tiny, but even tiny amounts of RNA can be detected by the massive amplification that goes on during PCR reactions. Detection of RNA encoding components of measles virus may be just that – detection of components of measles virus, not the virus.

By way of example, DNA encoding components of a mammoth have recently been amplified from a fossil. This might support the contention that there once were mammoths wherever the fossil that yielded the DNA was found. The amplification of mammoth DNA, however, does not indicate that there now are living mammoths at that site. Similarly, measles virus (vaccine strain) was supposedly found in Michelle's gut, but this does not mean that there is an active measles infection present. The bowel is a target organ for measles and, as MMR is a live vaccine, its ability to immunize depends on transient replication of its component live viruses. Evidence that the virus once was present in Michelle's gut would thus be expected and would not serve as proof of disease and, even less so, of ongoing disease.

After the 2002 biopsy, Michelle, who had been overweight and described as plump, lost weight and evidently vomited frequently. She is reported to have become physically weak and was experiencing significant abdominal pain. She was also exhibiting self-injurious behavior at the time, which is not unusual in children with autism, but which was attributed to her abdominal pain. At the urging of Dr. Krigsman, her current gastroenterologist, Michelle was admitted to a hospital in Yuma, Arizona to acquire a feeding jejunostomy tube (8/6/03), through which nutrients, calories, and medications could be administered. It is not clear why the tube was placed in the

jejunum, rather than in the stomach, which was what had originally been contemplated by her attending physicians. She is said to have transiently lost vision during the hospital stay; however, she was not given a complete ophthalmological evaluation. Because of easy bruising, a vitamin-K-dependent clotting disorder was diagnosed (although a mention is made of not knowing the meaning of the results of measurements of prothrombin time), which was corrected by oral vitamin K. This disorder was attributed to malnutrition, which in turn was attributed to her gastrointestinal disorder. At the time, her doctor, Robert Sheets, considered a diagnosis of Crohn's disease, but it was not confirmed and a serum level of tumor necrosis factor alpha (4/4/04) was measured and found to be normal. Michelle was also treated for conjunctivitis and ankle swelling. Juvenile rheumatoid arthritis (JRA) was considered as a possible diagnosis but not ruled out.

Michelle was said to have been sufficiently stabilized by her treatment in Yuma to travel to New York, a month after her jejunal tube was placed, to allow Dr. Krigsman to carry out upper and lower endoscopies. An aphthous ulcer was found in the sigmoid colon, which Dr. Krigsman (report, p. 3) said to be "characteristic of inflammatory bowel disease". An aphthous ulcer in the rectum or colon is also associated with the preparation of patients for colonoscopy with sodium phosphate (Driman and Preiksaitis, 1998) and thus is a common finding that requires confirmation by other means to enable a diagnosis of IBD to be made. Biopsies revealed no significant inflammatory pathology; therefore, a tissue diagnosis of IBD was not obtained. The patient is said to have had an elevated level of antibodies to the E. Coli protein, ompC. This would be consistent with, but not diagnostic of, Crohn's disease, because over a third of the ulcers that form in that

condition are colonized by E. coli and elevated antibodies to ompC are present in nearly half of Crohn's patients (Rolhion et al., 2007). Simply finding an elevation of this antibody, however, is not sufficient to diagnose Crohn's disease, although the antibody to ompC is useful in IBD diagnosis as part of a panel of IBD diagnostic tests, which are available, for example from Prometheus Laboratories*, and provide diagnostic predictions. One cannot say, therefore, as Dr. Krigsman does in his report (p. 3), that "Serology for inflammatory bowel disease was elevated (anti-ompC)". The serology is not diagnostic even when ompC is elevated.

Despite the fact that the diagnosis was not confirmed by biopsy and despite the lack of a backup to the observation of an elevated level of anti-ompC, Michelle was treated with 5-ASA and steroids. Predictably, she felt better, as most people do upon treatment with steroids, but predictably also she ultimately manifested the unfortunate side effects of steroid therapy, which in Michelle's case included osteoporosis. The steroids, however, helped the arthritis of the ankles and it is said to have normalized her stool. Steroids were thus discontinued and she was treated with 6-mecaptopurine. That drug was thought to have helped, but it too was stopped because of elevation of pancreatic enzymes (lipase) in her serum. Pancreatitis is a known untoward effect of 6-mecaptopurine therapy and the incidence of 6-mecaptopurine-induced pancreatitis is increased in IBD (Weersma et al., 2004), although serial CT imaging and ultrasound did not show evidence of chronic pancreatitis. Because restriction of her feedings to an elemental formula and oral 5-ASA did not control her symptoms, she was given Remicade (Infliximab; a monoclonal antibody against tumor necrosis factor). Remicade

* **Prometheus**, 9410 Carroll Park DriveSan Diego, CA 92121

has to be given intravenously; therefore, a local gastroenterological group was enlisted to help so that Michelle could be treated at her home in Arizona. This necessitated yet another upper and lower endoscopy on 6/8/06, which found another aphthous ulcer, this time in the transverse colon. Again, the lesion was photographed and lymphonodular hyperplasia was once more observed. As noted above, however, the aphthous ulcer detected in the transverse colon could have been caused by the preparation for colonoscopy but now it could also reflect the treatment with 5-ASA that Michelle received. Capsule endoscopy revealed multiple aphthous ulcers in the small intestine, which were interpreted as indicative of small bowel IBD, although the possibility that their presence was caused by 5-ASA and Remicade (which appears, according to the dates in Dr. Krigsman's report, to have been started prior to the endoscopic examination) was not excluded. Histopathology of both the upper and lower gastrointestinal tract were reported as unremarkable. As was true of prior biopsies taken during earlier endoscopies, biopsies of the bowel failed to confirm the existence of any form of IBD. The biopsy slides were reviewed by pathologists at UCLA, who concurred. The unremarkable nature of the biopsies can thus safely be taken as definitive. Despite the absence of evidence of IBD in the tissue findings, Remicade treatment was begun on 6/4/04 and Michelle's response was interpreted as a good one with respect to ankle swelling, limping, diarrhea, and overall irritability. The response to Remicade does not support a diagnosis of IBD because the severity of the symptoms of other inflammatory conditions, including JRA, may improve with Remicade. Unfortunately, Michelle developed epilepsy and fractured a tibia in October of 2005 in an accident associated with a seizure. Remicade was thereupon discontinued out of fear that it might interfere with healing of the fracture.

Michelle's other conditions are not limited to autism and the gastrointestinal tract. She also has seizures, arthritis, uveitis, and glaucoma. The arthritis has not been thoroughly characterized because it has been diagnosed as an IBD-related arthropathy. This seems odd because there is no reason to diagnose either Crohn's disease or ulcerative colitis in Michelle. There has never been a tissue diagnosis of IBD. The presumption, beginning with Dr. Krigsman, is that Michelle, who shows evidence of some inflammatory condition, must have "autistic enterocolitis" or "ASD-GI". Gastroenterologists as a scientific community do not recognize either of these as a diagnosis or descriptive of a unique or discrete medical condition. These terms have been used by a small group of physicians who believe that MMR causes autism to refer to the gastroenterological condition described by Dr. Wakefield and his collaborators (Chadwick et al., 2002; Furlano et al., 2001; Torrente et al., 2002; Uhlmann et al., 2002; Wakefield, 2002; Wakefield et al., 2005; Wakefield and Montgomery, 2000; Wakefield et al., 1998). The focus on these two "conditions" by her treating physicians has led to intensive administration of potentially toxic agents to treat IBD.

There has not been a search for other etiologies that might have benefited Michelle had they been found. It therefore would be inappropriate to categorically conclude that Michelle's gut-related problems are solely due to a GI disorder as opposed to an unusual eating pattern stemming from her autism. Autism is associated with dietary abnormalities and refusals to eat on the part of patients.

Etiology

In his original theory, summarized by Dr. Wakefield in 2000 in response to a request for clarification by the *New Challenges in Childhood Immunizations Conference (Halsey and Hyman, 2000)*, Wakefield proposed:

—1. "Atypical patterns of exposure to measles virus, including a close temporal association with another infection, are a risk factor for chronic intestinal inflammation."

—2. "There are factors, such as age, sex, and nature of concurrent exposure(s), that influence the phenotype of the intestinal pathology that develops i.e., Crohn's disease, ulcerative colitis, or autistic enterocolitis."

—3. "In children with autistic enterocolitis, persistent measles virus infection of the ileal lymphoid tissue causes chronic immune mediated pathology in the intestines."

—4. "Associated changes in intestinal permeability and altered peptidase activity allow neurotoxic intestinal products (e.g., exorphins) to reach the brain, which is particularly susceptible to permanent damage during times of rapid cerebral development such as infancy."

—5. "In susceptible children (possibly for reasons of age, immune status, or genetic background) MMR vaccine is an atypical pattern of measles exposure that represents a significantly increased risk for intestinal infection and associated developmental regression compared with the monovalent vaccine, or natural infection.)"

—6. “Accordingly, the widespread use of MMR immunization is a major determinant of the apparent (now substantiated) increase in rates of autism.”

This theory has now been thoroughly discredited. The epidemiological evidence against it, as noted previously, is overwhelming (Chen et al., 2004; Dales et al., 2001; Fombonne et al., 2006; Honda et al., 2005; Madsen et al., 2002; Mangel and Koegel, 1984; Smeeth et al., 2004). The molecular underpinning, that RNA encoding components of measles virus persists in the bowel of children vaccinated against MMR has been undone by recent careful studies that show that measles virus, in fact, does not persist after MMR vaccination (Afzal et al., 2006; D'Souza et al., 2006; Katz, 2006; Shevell and Fombonne, 2006).

The postulated change in the properties of digestive enzymes would require unprecedented events to occur. Certainly, the DNAs encoding these enzymes cannot react to measles infection by altering their sequences so as to acquire the novel ability to cut toxic peptides out of the ingested proteins within which the sequence of their component amino acids are found. Even if such peptides were to appear as a result of the action of luminal endopeptidases (enzymes that digest proteins from within their amino acid sequence, as opposed to exopeptidases, which digest proteins at the ends of the sequence), the peptidases of the gut wall would not let them enter the body without further digestion. The enterocytes (intestinal cells that border the lumen of the small intestine, where nutrient absorption largely occurs) that line the bowel have finger-like projections facing the lumen of the gut that bristle with peptidases. These cells normally see products of luminal digestion of proteins, which are amino acids and small peptides

(consisting of 2 or 3 linked amino acids). The amino acid products of digestion are taken into the cells. Dipeptides and tripeptides that escape peptidase breakdown can enter enterocytes as a result of the action of PepT1, a peptide transporter; however, on doing so, they encounter further peptidases in the cytosol of the enterocytes and thus, they too are broken down into single amino acids. The amino acids formed in the enterocytes, or transported into them, are subsequently transported out of these cells at their base (into the body) by means of at least 3 transporters. There are no transporters to move peptides out of the base of enterocytes. It is thus unlikely that toxic peptides, which are large molecules, will be formed by digestive enzymes in the gut or, if they are, that they will enter the body by going through the cells that line the bowel. In Michelle, these lining cells (enterocytes) are clearly functioning adequately, because were they not, Michelle would manifest malabsorption syndrome, which she does not.

Could toxic peptides be absorbed by entering the body between the cells that line the intestinal lumen? That route is normally plugged by an intercellular modification called a tight junction. Measles virus infection has not been demonstrated to cause these junctions to deteriorate. If one were to assume, nevertheless, that measles virus could open these junctions, then large molecules in the wall of the gut, which are critical to maintaining homeostasis, would leak into the lumen of the bowel. These essential molecules in the intestinal lumen would thus be irretrievably lost into the lumen of the bowel, and the body itself would swell (exudative enteropathy). Michelle has manifested no evidence of exudative enteropathy. To allow significant leakage of large toxic molecules into the body without losing critical large molecules into the gut lumen,

measles infection would have to turn the tight junctions between her enterocytes into one-way valves. This is not within the realm of possibility.

Even if all of the events listed above were to occur, the liver, which is specialized to remove toxic peptides, and is good at doing so, would have to be unable to act normally or would have to specifically make an exception for peptides that Dr. Wakefield postulates cause autism. Michelle is not jaundiced; therefore, the ability of her liver to detoxify molecules is intact. The alternative that the liver might make an exception for those peptides that might purportedly cause autism has no basis in medical science.

If the postulated toxic peptides were, through no mechanism known to science, to form, enter the body, and bypass the liver, they would still not be able to get through the blood-brain barrier without a transporter specialized to permit this toxic action to occur. No such transporter is known, nor has measles infection ever been demonstrated to be able to create one. Michelle has no evidence of a defect in her blood-brain barrier function.

In fact, the evidence of bowel inflammation in Michelle's case is equivocal. Michelle has not been shown to have Crohn's disease and probably does not. In fact, there is no tissue diagnosis (pathology) of any form of IBD. Non-specific observations that might have other reasons for being are interpreted through the lens of what appears to be preconceptions about her problem as indicative of "ASD-GI". Michelle may be subject to an undefined inflammatory condition, JRA, or some another. The inflammatory markers in her serum are merely signals of inflammation somewhere in her body – not necessarily the gut. Michelle has occasionally had symptoms of arthritis and a

diagnosis of JRA has been considered. Inflammatory markers in serum would be expected with arthritis or JRA. Inflammation has never been seen in the many biopsies obtained from Michelle's gut. Improvement as a result of tube feeding with an elemental formula is not, as alleged, evidence that Michelle suffers from IBD.

"ASD-GI" and "autistic enterocolitis" are not gastroenterological disease entities. Nor are they recognized by the gastroenterological community as a "specific" form of autism with a gastroenterological basis. Most gastroenterologists do not use these terms in diagnosis, nor do they recognize that such a discrete disease entity exists. As explained, the mechanism purported to cause "ASD-GI" or "autistic enterocolitis" lacks any basis in gastroenterology specifically or medical science generally.

Petitioners' experts attribute Michelle's autism to a chronic measles infection of the brain – a postulate for which there is no evidence. While an intestinal biopsy yielded a report of RNA encoding components of measles virus, albeit probably with primers that give false positive results (and represent an observation that cannot be replicated by careful studies by independent investigators), there is no record of the detection of any component of measles virus in Michelle's brain or cerebral spinal fluid. When chronic measles virus infection occurs in the brain, it gives rise to subacute sclerosing panencephalitis (SSPE). Michelle clearly does not have SSPE; she has autism. That two are readily distinguishable.

Dr. Krigsman concludes that Michelle has "an undisputed case of ASD-GI". This conclusion is unprofessional; both Michelle's diagnosis and the entity itself are disputed. Michelle has not been definitively shown to be suffering from IBD. The diagnosis,

"ASD-GI", is not generally accepted as an entity. It is an invention of Andrew Wakefield and awaits acceptance by more than his followers.

Summary

1. There is no supportable evidence that MMR vaccination leads to IBD.

2. There is no supportable evidence that MMR vaccination leads to autism.

3. There is no evidence that MMR caused Michelle Cedillo to acquire a gastrointestinal illness, nor that that there is a chronic measles virus infection in Michelle's gut.

4. There is no evidence that MMR caused Michelle Cedillo to become autistic.

5. There is no evidence that Michelle Cedillo has a chronic infection with measles virus.

6. There has been no pathological documentation that Michelle Cedillo suffers from inflammatory bowel disease and no indication that she manifests Crohn's disease or ulcerative colitis.

7. Aphthous ulcers and hyperplasia of lymphoid tissue were described in Michelle Cedillo's bowel but are non-specific changes and, in the absence of a tissue diagnosis, insufficient to support the conclusion that she has IBD. The repeatedly negative biopsies detract from the clinical impression of IBD.

8. There is no credible evidence to indicate that Michelle Cedillo's autism or other disabilities are causally related to her vaccination against MMR.

Sincerely,

Michael D. Gershon, M.D.

Department of Pathology & Cell Biology

Columbia University

College of Physicians and Surgeons

References Cited

1. Afzal, M. A., and Minor, P. D. (2002). Vaccines, Crohn's disease and autism. *Mol Psychiatry* **7 Suppl 2,** S49-50.

2. Afzal, M. A., Ozoemena, L. C., O'Hare, A., Kidger, K. A., Bentley, M. L., and Minor, P. D. (2006). Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunization schedule of UK. *J Med Virol* **78,** 623-30.

3. Chadwick, V. S., Chen, W., Shu, D., Paulus, B., Bethwaite, P., Tie, A., and Wilson, I. (2002). Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* **122,** 1778-83.

4. Chen, W., Landau, S., Sham, P., and Fombonne, E. (2004). No evidence for links between autism, MMR and measles virus. *Psychol Med* **34,** 543-53.

5. Chitkara, D. K., Talley, N. J., Weaver, A. L., Katusic, S. K., De Schepper, H., Rucker, M. J., and Locke, G. R., 3rd. (2007). Incidence of presentation of common functional gastrointestinal disorders in children from birth to 5 years: a cohort study. *Clin Gastroenterol Hepatol* **5,** 186-91.

6. D'Souza, Y., Fombonne, E., and Ward, B. J. (2006). No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder. *Pediatrics* **118,** 1664-75.

7. Dales, L., Hammer, S. J., and Smith, N. J. (2001). Time trends in autism and in MMR immunization coverage in California. *Jama* **285,** 1183-5.

8. Driman, D. K., and Preiksaitis, H. G. (1998). Colorectal inflammation and increased cell proliferation associated with oral sodium phosphate bowel preparation solution. *Hum Pathol* **29,** 972-8.

9. Fombonne, E., and Chakrabarti, S. (2001). No evidence for a new variant of measles-mumps-rubella-induced autism. *Pediatrics* **108,** E58.

10. Fombonne, E., Zakarian, R., Bennett, A., Meng, L., and McLean-Heywood, D. (2006). Pervasive developmental disorders in Montreal, Quebec, Canada: prevalence and links with immunizations. *Pediatrics* **118,** e139-50.

11. Franken, E. A., Jr. (1970). Lymphoid hyperplasia of the colon. *Radiology* **94,** 329-34.

12. Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A., Davies, S. E., Berelowitz, M., Forbes, A., Wakefield, A. J., Walker-Smith, J. A., and Murch, S. H. (2001). Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr* **138,** 366-72.

13. Gershon, M. D. (1998). "The Second Brain." Harper Collins, New York, N.Y.

14. Gershon, M. D., and Ross, L. l. (1962). Studies on the relationship of 5-hydroxytryptamine and the enterochromaffin cell to anaphylatic shock in mice. *J. Exp. Med.* **115,** 367-382.

15. Halsey, N. A., and Hyman, S. L. (2001). Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12-13, 2000. *Pediatrics* **107,** E84.

16. Honda, H., Shimizu, Y., and Rutter, M. (2005). No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry* **46,** 572-9.

17. Katz, S. L. (2006). Has the measles-mumps-rubella vaccine been fully exonerated? *Pediatrics* **118,** 1744-5.

18. Kawashima, H., Mori, T., Kashiwagi, Y., Takekuma, K., Hoshika, A., and Wakefield, A. (2000). Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. *Dig Dis Sci* **45,** 723-9.

19. Kokkonen, J., and Karttunen, T. J. (2002). Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? *J Pediatr Gastroenterol Nutr* **34,** 42-6.

20. LeBaron, C. W., Sullivan, B. J., Beck, C., and Gargiullo, P. (2006). Evaluation of potentially common adverse events associated with the first and second doses of measles mumps rubella vaccine. *Pediatrics* **118**, 1422-30.

21. Lucendo, A. J., Navarro, M., Comas, C., Pascual, J. M., Burgos, E., Santamaria, L., and Larrauri, J. (2007). Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* **31,** 598-606.

22. Madsen, K. M., Hviid, A., Vestergaard, M., Schendel, D., Wohlfahrt, J., Thorsen, P., Olsen, J., and Melbye, M. (2002). A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med* **347,** 1477-82.

23. Mangel, A. W., and Koegel, A. (1984). Effects of peptides on gastric emptying. *Am J. Physiol.* **246,** G341-G345.

24. Martin, C. M., Uhlmann, V., Killalea, A., Sheils, O., and O'Leary, J. J. (2002). Detection of measles virus in children with ileo-colonic lymphoid nodular hyperplasia, enterocolitis and developmental disorder. *Mol Psychiatry* **7 Suppl 2,** S47-8.

25. Murch, S. H., Anthony, A., Casson, D. H., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Valentine, A., Davies, S. E., and Walker-Smith, J. A. (2004). Retraction of an interpretation. *Lancet* **363,** 750.

26. Riddlesberger, M. M., Jr., and Lebenthal, E. (1980). Nodular colonic mucosa of childhood: normal or pathologic? *Gastroenterology* **79,** 265-70.

27. Rolhion, N., Carvalho, F. A., and Darfeuille-Michaud, A. (2007). OmpC and the sigma(E) regulatory pathway are involved in adhesion and invasion of the Crohn's disease-associated Escherichia coli strain LF82. *Mol Microbiol* **63,** 1684-700.

28. Rossi, T. (1988). Endoscopic examination of the colon in infancy and childhood. *Pediatr Clin North Am* **35,** 331-56.

29. Shaoul, R., Eliakim, R., Tamir, A., and Karban, A. (2006). Ileal lymphonodular hyperplasia is not associated with NOD2/CARD15 mutations. *J Pediatr Gastroenterol Nutr* **43,** 30-4.

30. Shevell, M., and Fombonne, E. (2006). Autism and MMR vaccination or thimerosal exposure: an urban legend? *Can J Neurol Sci* **33,** 339-40.

31. Smeeth, L., Cook, C., Fombonne, E., Heavey, L., Rodrigues, L. C., Smith, P. G., and Hall, A. J. (2004). MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* **364,** 963-9.

32. Torrente, F., Ashwood, P., Day, R., Machado, N., Furlano, R. I., Anthony, A., Davies, S. E., Wakefield, A. J., Thomson, M. A., Walker-Smith, J. A., and Murch, S. H. (2002). Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Mol Psychiatry* **7,** 375-82, 334.

33. Uhlmann, V., Martin, C. M., Sheils, O., Pilkington, L., Silva, I., Killalea, A., Murch, S. B., Walker-Smith, J., Thomson, M., Wakefield, A. J., and O'Leary, J. J. (2002). Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol* **55,** 84-90.

34. Wakefield, A. J. (2002). Enterocolitis, autism and measles virus. *Mol Psychiatry* **7 Suppl 2,** S44-6.

35. Wakefield, A. J., Ashwood, P., Limb, K., and Anthony, A. (2005). The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. *Eur J Gastroenterol Hepatol* **17,** 827-36.

36. Wakefield, A. J., and Montgomery, S. M. (2000). Measles, mumps, rubella vaccine: through a glass, darkly. *Adverse Drug React Toxicol Rev* **19,** 265-83; discussion 284-92.

37. Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E., and Walker-Smith, J. A. (1998). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children [see comments]. *Lancet* 351, 637-41.

38. Weersma, R. K., Peters, F. T., Oostenbrug, L. E., van den Berg, A. P., van Haastert, M., Ploeg, R. J., Posthumus, M. D., Homan van der Heide, J. J., Jansen, P. L., and van Dullemen, H. M. (2004). Increased incidence of azathioprine-induced pancreatitis in Crohn's disease compared with other diseases. Aliment Pharmacol Ther 20, 843-50.