UNITED STATES
COURT OF FEDERAL CLAIMS

THERESA CEDILLO AND MICHAEL CEDILLO, AS PARENTS AND NATURAL GUARDIANS OF MICHELLE CEDILLO,	)	
Petitioners,	)	
v.	)	Docket No.: 98-916V
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Pages: 859 through 1023

Place: Washington, D.C.

Date: June 14, 2007

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1220 L Street, N.W., Suite 600
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(202) 628-4888
hrc@concentric.net

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

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SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Ceremonial Courtroom
National Courts Building
717 Madison Place NW
Washington, D.C.

Thursday,
June 14, 2007

The parties met, pursuant to notice of the Court, at 9:02 a.m.

BEFORE: HONORABLE GEORGE L. HASTINGS, JR.
HONORABLE PATRICIA CAMPBELL-SMITH
HONORABLE DENISE VOWELL
Special Masters

APPEARANCES:

For the Petitioners:

SYLVIA CHIN-CAPLAN, Esquire
KEVIN CONWAY, Esquire
RONALD C. HOMER, Esquire
Conway, Homer & Chin-Caplan, P.C.
16 Shawmut Street
Boston, Massachusetts 02116
(617) 695-1990

APPEARANCES: (Cont'd.)

Also for the Petitioners:

CLIFFORD J. SHOEMAKER, Esquire
Shoemaker & Associates
9711 Meadowlark Road
Vienna, Virginia 22812
(703) 281-6395

For the Respondent:

VINCENT J. MATANOSKI, Esquire
ALEXIS BABCOCK, Esquire
U.S. Department of Justice
Civil Division
Torts Branch
P.O. Box 146
Ben Franklin Station
Washington, D.C. 20044-0146
(202) 616-4122

C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Petitioners:					
Vera S. Byers	862	934	1010	1015	--

P R O C E E D I N G S

(9:02 a.m.)

SPECIAL MASTER HASTINGS: All right. We're going to call this morning session to order here.

I understand that your next witness is going to be Dr. Byers, and she's already on the witness stand so that, Ms. Chin-Caplan, when you're ready go ahead with your direct.

Dr. Byers, would you raise your right hand, please?

Whereupon,

VERA S. BYERS

having been duly sworn, was called as a witness and was examined and testified as follows:

SPECIAL MASTER HASTINGS: Please go ahead, Ms. Chin-Caplan.

MS. CHIN-CAPLAN: Thank you, Special Master.

DIRECT EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. Byers, could you kindly state your name for the record, please?

A Yes. Vera S. Byers.

Q Dr. Byers, would you kindly give the Court a brief description of your educational background from college?

A From college?

Q From college.

A Yes. I graduated from UCLA with a degree in Microbiology, because at that time we didn't have immunology. I then got a Master's degree in Protein Chemistry, I think.

I have an M.D. from UCSF with boards in Internal Medicine, a Ph.D. in Basic Immunology, a fellowship in Protein Chemistry, another three-year fellowship in Clinical Immunology again from UCSF. I think that's it.

Q And after you finished your M.D. did you have an internship?

A Yes. That's why I said boards in Internal Medicine. That requires an internship and then two additional years of internal medicine.

Q And are you board certified?

A Yes, I am.

Q And what is your board certification in?

A Internal Medicine.

Q Doctor, could you kindly describe your work experience since your graduation?

A That's a long time ago. I joined the faculty at UCSF initially in the Department of Medicine and then in the Department of Dermatology.

I did research in tumor immunology initially. I was one of the founders of the field, at least one of the initial workers in the field, because I was doing clinical trials in osteogenic sarcoma, which is a cancer of young teenagers, using immunotherapy. People were not doing that at the time. We didn't really know about immunotherapy at the time.

Then I worked on immunodermatology, particularly poison oak. At one time I was considered the world's expert in poison oak and ivy dermatitis, which my medical student colleagues thought was amusing because they didn't think it was very important.

SPECIAL MASTER HASTINGS: Doctor, can I have you maybe pull those microphones a little bit closer to you? The other one too if you can. It's laying on the table there. Great. Thank you.

THE WITNESS: Is this better?

SPECIAL MASTER HASTINGS: I hope so.

THE WITNESS: Okay. Let's see. Where was I?

MS. CHIN-CAPLAN: Poison oak.

THE WITNESS: Poison oak, yes. So I worked on poison oak and basically immunodermatology

psoriasis for a while, and then when I finished my residency I continued on the faculty at UCSF, but I also joined a company called Xoma Corporation, which was one of the fist biotech companies, and then also joined the faculty at the University of Nottingham in England and continued doing work in primarily cancer research, but also monoclonal antibodies.

I was the inventor of the first monoclonal antibody to be put into clinical trials initially at the University of Nottingham and then later on at Xoma, and I also was the inventor of the first of the antibodies that ultimately culminated in the ones that are now used for leukemias and lymphomas.

The antibody was called H65RTA because it had ricin A chain attached to it. We were using it initially in graft versus host disease, for which I received approval from the FDA Scientific Advisory Board for use in a salvage therapy for GVHD, and then I put it into clinical trials in a wide variety of autoimmune disease ranging from Type 1 diabetes through Crohn's disease through multiple sclerosis, rheumatoid arthritis, et cetera.

Then after a time I started a company, an allergy company, again using biologic-based therapies to more rapidly desensitize people for classic

allergies. We were looking at both poison oak, no surprise, and dust mites, which was DRP-1, and then I moved on to being a consultant, and that's what I've been doing for probably the last 15 years.

I split my time between working as a medical toxicologist, so I go out. I'm usually contacted by people, usually attorneys, who are looking at large populations of people who have been exposed potentially to environmental chemicals, and they would like me to go out and see whether or not there is a signature.

For example, the first one of those I did was there was a case in Woburn, Massachusetts, where the people were exposed to trichloroethylene in the water and they were developing leukemias, and the question was whether or not the trichloroethylene could be attributed to the water.

Later they wrote a book about it. Jonathan Harr wrote a book called *Civil Action*, and they made a movie out of it. I think it's one of the first so-called clusters that has ever actually been confirmed for an etiologic agent because the Massachusetts Department of Public Health or something went in later on, and they did a large study comparing East Woburn with West Woburn, one of which had TCE in the water

and other did not. They confirmed that in fact I was correct.

BY MS. CHIN-CAPLAN:

Q Do you consult to drug manufacturers as well?

A Oh, sorry. Yes. The other part of my time I spend being a consultant to biotech companies. I specialize in biologics. For example, let's see, I worked with a vaccine for multiple sclerosis with gamma interferon for atopic dermatitis, ran a large study in that.

The largest chunk of time I guess I spent was at Immunex in Seattle. I was there for three years on the team that got Enbrel, which is basically a TNF sponge, and it was approved for rheumatoid arthritis, thoriatic arthritis, Still's disease, et cetera.

Our competitor, Remicade, you probably know Remicade better because it also had the same profile with the addition of it's also effective in Crohn's disease.

Q Doctor, are you currently consulting to a biotech company?

A Yes. At the moment I've been primarily working with a company called Hutchison MediPharma,

which is based out of Shanghai.

Their mandate is about a year and a half ago the FDA finally approved regulations by which we can take herbal mixtures and put them in clinical trials in the United States. We didn't have the release criteria before.

Hutchison, one of their main areas of interest is to take classic Chinese herbs and then put them in clinical trials in the United States and so at the moment I'm involved with the clinical trial of one of their herbs in Crohn's disease in the United States and in ulcerative colitis in China.

Q Doctor, you indicated that you had an appointment at the University of Nottingham in London?

A No, no. In Nottingham, England.

Q What was that appointment?

A That was as a senior lecturer, which is basically it's probably like an associate professor, maybe a little bit higher than an associate professor, and I held that position from around 1984 until about 2000.

One of the main reasons for the appointment is that that was the main place that I was conducting my research. That's where my lab was.

Q You indicated that you had a clinical

practice as well?

A Yes. I practiced allergy and immunology from about 1981 through something like 1998, 2000, something like that, seeing patients with a variety of diseases, both pediatric and adult, with a wide variety of immunologic and allergic conditions.

Q And have you operated different types of clinical laboratories to observe certain patient populations?

A Yes. I set up and ran the Immunology Division of the LCL from approximately something like 1977 through 1979, something like that. I set up their Immunopathology Division and ran it during that time.

Q You said LCL. What does LCL stand for?

A Lavin Clinical Labs.

Q And did you run any other clinical labs?

A Well, obviously I ran my own clinical labs when I was doing full-time academic research, and then also I was involved in much of the human work that was done at the University of Nottingham.

Q Did you have any relationship with the AIDS Clinic at UCSF?

A I forgot. Thank you. It wasn't at UCSF. We founded the largest AIDS clinic in San Francisco.

If I remember rightly, I think it was called Positive Action. Positive Action.

The concept was it was in the very early days of AIDS before the protease inhibitors and so AIDS was a really devastating disease. The people who had HIV disease were going out and taking lots and lots of different drugs on their own and so the promise to them was that we would monitor the drugs that they were taking, as well as suggest those of our own, but they had to tell us what they were taking.

We wound up having a very good relationship with the HIV community and were actually responsible, I think we were at least in part responsible, for the fast track drug application that we have now.

I do know for sure that we were responsible for taking away the enmity that the gay community had between the governmental agencies and the drug companies because we just kind of involved them in there, and that's really all they wanted.

Q Doctor, have you published any articles?

A Oh, yes. I've probably got about 200 published articles, but I'd have to check my bibliography to make sure because I haven't thought about it for a while.

Q You indicated that you do research. What is

the subject of your research?

A When? Now or then or what?

Q Currently.

A Currently the main research is probably on these populations that I was telling you that are exposed to toxic chemicals, as well as the research on the herbs that I'm running with the Chinese company.

Q And in the past did you have other research interests?

A Well, primarily tumor immunology and chemical carcinogenesis in general.

Q So you were doing cancer research?

A Yes. Well, the part of the immune system that is responsible for controlling cancer, yes.

Q Do you sit on any national panels at all?

A Oh, primarily the NIH committee called the SBIR, Small Business Innovative Research. I've been on that for a long time, like about 15 years.

Q Do you hold any patents, Doctor?

A I probably have about 10.

Q And do you sit on any editorial review boards?

A Yes. Well, I served on Cancer Drugs and then Cancer, Immunology and Immunotherapy until about two years ago.

Q Doctor, at some point in time were you asked to review the medical records of Michelle Cedillo?

A Yes, I was.

Q Doctor, when you reviewed the medical records of Michelle Cedillo what were you looking for?

A I was asked to give an opinion as to why the measles virus had persisted in her body. I was already given information that it had. My conclusion was that she had and has a dysregulated immune system.

I was asked then to list the known causes for immune dysregulation in Michelle, that particular child, and I concluded that it was a combination of genetics and the measles virus vaccination and the thimerosal-containing vaccines that she had received.

I was asked to opine as to the results of the persistent measles infection or of the persistent measles virus, and I found that I could attribute her chronic gut inflammation and opine that she would be expected to have CNS pathology as a result of that.

Q Now, Doctor, how does one work up a child who has an immune dysfunction?

A If I could have the next slide?

SPECIAL MASTER HASTINGS: All right. Let's stop for a minute here now. Dr. Byers, like the previous Petitioners' witnesses, has a slide

presentation for us.

We have paper copies of it. Let's mark those, Ms. Chin-Caplan, as Petitioners' Trial Exhibit I think we're at No. 9, are we not?

Dr. Byers had just been referring to page 1 of that group, so now we're going to move to page 2 of that, I understand. Go ahead, Dr. Byers.

BY MS. CHIN-CAPLAN:

Q So, Doctor, when one evaluates a child for immune dysregulation what would you do as a clinical person?

A You would take a family history. You would be particularly interested in a family history of immune disorders. You would take a personal history.

You would be particularly interested in a history of frequent or unusual infection, and with children that's fairly easy because the CDC has published criteria by which how many infections a child of a given age should expect to have.

You're particularly interested in an infection that caused the child to be taken to the doctor, because that means that the family is concerned enough about the child, and about cases when the child has been put on an antibiotic because that means that the physician is concerned enough about the

infection.

Other things you would look at would be aberrant reactions to vaccines and chronic inflammatory conditions.

Q And when you looked at Michelle's history did you notice any factors which would lead you to believe that she had a dysregulated immune system?

A I did.

Q And what were those factors?

A I noticed clinically that she certainly had an aberrant reaction to the MMR vaccine and that she also had at least one, if not more, chronic inflammatory conditions.

In her case I did not find that she had a history of frequent or unusual infections, and her only family history was notable for just routine allergies.

Q Doctor, once you take that family history and you determine that there might be something there worth evaluating, what would you do next?

A The next thing you would do would be laboratory tests.

Q What laboratory tests would you run, Doctor?

A As shown on Slide 3, this is just a fairly routine set of labs, so it's a CBC, which is a

complete blood count; a differential, which is the number, the percent of modified macrophages, T cells, B cells, et cetera, in the lymphocyte population; a chemistry panel, which would include tests of liver function, of renal function, et cetera; and then a urinalysis.

Then the B and T cells with the subset analysis; serum immunoglobulin levels, and in that case you're particularly looking for something simple like common variable immunodeficiency disorder because there's a treatment for that.

And then response to both ubiquitous antigens -- a ubiquitous antigen is something that like 90 percent of the population has been exposed to, so you know that if you check mitogenesis, for example, you know that those people have been sensitized to that or should have been sensitized, and if you get a negative reaction then you know that there's something abnormal with the immune system -- and then also a response to using the nonspecific mitogens.

The nonspecific mitogens are things like pokeweed mitogen, Concanavalin A, et cetera. Those are things that are just nonspecific stimulants of the B cells or the T cells that everybody is going to

react to if they have normal reactions.

In other words, when you're looking at your B and T cells you're just looking at the number of cells, but you're not asking whether they can function properly. When you're looking at the response to the antigens, you're asking whether not only are they there, but can they also function properly.

Q So, Doctor, the last three, the B and T cells with subset analysis, the serum immunoglobulin levels with subclass analysis and the response to the antigens, vaccine and nonspecific mitogens. Are they are considered part of an immune panel?

A Yes, they are.

Q Now, to your knowledge was Michelle Cedillo's immune system evaluated?

A It was, and it was really fortuitous because it's my understanding that the only reason that we have these data so early in the disease process is because her mom wanted to see whether or not she would qualify for intravenous gammaglobulin and so that's the only reason that we got all of these antigens.

Later on she had had so many treatments, steroids, et cetera, that you really could not have gotten a good assessment.

Q And do you know who she was evaluated by?

A Yes. Dr. Gupta.

MS. CHIN-CAPLAN: Okay. For the Court, Dr. Gupta's record is contained at Petitioners' Exhibit 3.

BY MS. CHIN-CAPLAN:

Q So, Doctor, when you evaluated the medical records and everything, what history did you obtain about Michelle?

A I found, as you can see itemized on Slide 4, that she was the product of a normal pregnancy and delivery, that she had had viral syndromes at age three and seven months, which were not unduly frequent. She did have an allergy to amoxicillin.

She had received her MMR vaccination at age 15 months, and then a very colorful and dramatic set of circumstances occurred, which is that seven days later she developed a high fever, which essentially lasted for two weeks.

It waxed and waned a little bit, but, I mean, her mom is describing temperatures of up to 106, and at the end of that two-week period she was documented in the clinic to still have a temperature of 100.6, so that is not only a very unusually long interval, but the extent of the reaction is very high.

It's at the time that would be expected. It's just that it lasted for a long time, and it was

very dramatically unusual.

Q Doctor, just to interrupt you for one minute, you said that it would be expected. Would the fever of 105, almost 106, be expected?

A No. The time at which it appeared is not unusual. It's not unusual to have a mild fever following the vaccination at about seven days.

Q When you say a mild fever, what is a mild fever?

A Under 100.

Q Thank you. And what other information did you obtain on Michelle's history from the medical records?

A That when the fever resolved it then was noted that she had diarrhea, which ultimately proved to be the beginning of her chronic inflammatory bowel disease, which she continues to suffer from.

Q Thank you. Doctor, you indicated previously that she saw Dr. Gupta for an immune workup. Is that true?

A That's correct.

Q Where is Dr. Gupta located?

A He's at UC-Irvine.

Q And is Dr. Gupta somebody whose reputation you are familiar with in the community?

A Yes. He's a well-known clinical immunologist.

Q Doctor, did you review that immune panel that was performed on Michelle by Dr. Gupta?

A Yes, I did.

Q Doctor, when you reviewed the records, what tests did Dr. Gupta run?

A Dr. Gupta did the tests that I had indicated on the previous slide, which I think was Slide 3 or 4.

Q And after reviewing those tests and looking at her clinical history, did you come to some conclusion about whether Michelle suffered from some immune dysfunction?

A Yes. I concluded that she suffers from immune dysregulation, and this is in part characterized by the TH1/TH2 skewing, which was described by Dr. Kennedy yesterday.

Q Doctor, subsequent to that immune workup did Michelle also demonstrate clinical evidence of immune dysregulation?

A Yes, primarily with the chronic inflammatory bowel disease, but also in the inability to clear the measles virus vaccine strain from her body.

Q With respect to the main workup that was performed by Dr. Gupta, could you go into the

specifics of what Dr. Gupta found?

A Well, the only thing on my slide that I pointed out are the laboratory abnormalities, so therefore she has an unusually low CD8 count, and as a result she has an elevated CD4:CD8 ratio. An elevated CD4:CD8 ratio is compatible with autoimmune disease.

Q Could you kindly describe to the Court the relationship between CD4 and CD8?

A Yes. Let me see. The normal CD4:CD8 ratio should be about 1.2, so in other words you have just about as many CD4s as you do CD8s.

In this case she has an abnormally low CD8 population. In those days I think we really did not understand, and maybe we still don't really understand, why that predisposes you, or at least is characteristics of, autoimmune disease, but that's what she had, so it's compatible with her chronic bowel inflammatory disease.

Q And, Doctor, you indicated she had an elevated CD20?

A Yes.

Q What is the significance of the elevated CD20?

A It just means that you've got abnormally elevated B cell precursors, and it could go along with

the abnormally elevated IgG2 and IgG4.

Q You indicate here also that she had a low response to specific and nonspecific mitogens?

A Yes. As I described before, it's one thing just to figure out how many cells are there, but you'd also like to know whether they're working properly and so if I could see the next slide?

SPECIAL MASTER HASTINGS: So we're leaving Slide 5 and going to Slide 6?

THE WITNESS: Yes. We may go back to Slide 5. You asked me for the function, so therefore I'm going to have to go through 7 or 8. There you go.

SPECIAL MASTER HASTINGS: So now we're on Slide 7?

MS. CHIN-CAPLAN: That's correct, Special Master.

SPECIAL MASTER HASTINGS: If one of you can try to mention the number as we get to it I won't have to interrupt you.

MS. CHIN-CAPLAN: Okay.

THE WITNESS: I'll do it. So as you can see, and I'm just going to give you numbers, but basically what you're looking at is when you're looking at these mitogen assays you're hitting a population of T cells in a test tube with something

that it should react to.

And then you're putting in radioactivity and you're comparing the radioactivity in the stimulated cultures with those of nonstimulated cultures, and then you're looking at your normal range, and you're doing the same thing.

In other words, you're taking a group of normal people from wherever you're going to get it, from the population served by your lab, and you are using exactly the same standard operating procedures and exactly the same equipment to run those people and establish what the value should be in a normal population, and then you are using that to compare the numbers that you get from your patients.

The main thing you need to look at is just look at the numbers which are outside the normal range. As you can see, the nonspecific mitogens that were abnormal here, that is the ones that everybody should respond to regardless to whether they've been exposed to the antigen or not, is something called ConA and the pokeweed mitogen, which are abnormally low.

I'm going to go over this fast because I know everybody is bored with lab tests. Then if you look at the specific antigens, that is which most of

the population has been exposed to, you can also see that she is low on mumps, candida and PPD.

BY MS. CHIN-CAPLAN:

Q So she was low on ConA, pokeweed mitogen, mumps and candida and PPD? Is that it?

A That's right.

Q Doctor, if you could go back to page 5? Was there one last abnormality noted in her immune workup?

A I'm sorry. Do you want 5 or 6?

Q Page 5. We didn't discuss the last one.

A Oh, sorry. I think I did. The fact that she has abnormally elevated IgG2 and IgG4, which is consistent with TH1/TH2 skewing.

I will just remind the Special Masters that Dr. Kennedy described that yesterday. What that does, you've got cross regulation. I'm sorry. You've got the TH1s that are responsible for other things killing virally infected cells, right, because antibodies can't reach the virus once it's in the cell and so therefore you need a T cell that can eat it up.

Your TH2s are also important, but they are responsible for immunoglobulins, specifically IgG2 and IgG4, and they cross regulate so therefore if you have TH1/TH2 skewing the reason that is bad is because the TH2s can sit on the TH1s and prevent them from working

as effectively as they should.

Q Doctor, you previously had indicated that they looked at the CD4 and CD8 ratio.

A That's right.

Q If we could go to page 6? Could you remind the Court what you indicated was the result of this bloodwork?

A Yes. You can see here that she has a normal level of CD4, but she has an abnormally low level of CD8. Therefore, that gives her an abnormally elevated CD4:CD8 ratio, which then is indicative of an autoimmune process.

Of course, maybe we didn't know back then because she had just started with this chronic bowel problem, but we now know that she does have a chronic autoimmune process.

Q Doctor, again the result of the CD20? What was the significance of that?

A The CD20 indicates that you've got an abnormally elevated precursor B cell population, which would be consistent with several things, but including some bone marrow toxicity.

Q Thank you.

A Maybe I should make a comment here just so that I can explain the colors of the slides.

The UCI laboratory normal range is indicated in blue here. The other ranges that have been used by Dr. McCusker?

Q Yes.

A Thank you. Include Hannet, Shearer and Gasparoni, and what she was trying to do is to give you normal ranges that are age specific.

While it's certainly correct that there are different normal ranges at the different ages, the problem is that you cannot compare a single result from one lab with results from a different lab. You have to compare it with that same laboratory and so that's why I have put in the UCI laboratory range in blue.

Q Doctor, what is the reason why you can't compare and apply the normals from one laboratory to another laboratory?

A First of all, even if you're doing it concomitantly the laboratories are using different reagents, different instruments, and so they're going to get different normal ranges.

In this case it's particularly difficult because the initial labs from Cedillo were done in I think 1997. For example, the range from Shearer was done in 2003, so to give you an example, let's see.

Shall we choose Kevin Conway again?

If Mr. Conway had gone in to his doctor in 1995 and said I have shortness of breath and they had found a suspicious lesion in the chest and the doctor said well, let's just follow it so come back in a year, and so Mr. Conway doesn't come back until 2000. Once again he has shortness of breath.

If the doc tries to do a CT scan again of the chest, unless there's been a really, really dramatic change in that you can't compare those two CTs because the laboratory will have gotten a better CT scanner in that five-year period.

So that's the second problem with this, which is that you're trying to compare lab tests that were done in 1997 when our knowledge of immunology was actually pretty poor and our reagents weren't great either, with something like a normal range in the year 2003.

Q And the ranges that Michelle Cedillo's lab results came from was the one from the UC-Irvine Laboratory?

A Yes. It's the same laboratory where here tests were done.

Q Okay. And those were the tests that were ordered by Dr. Gupta?

A That's right, and those were the normal ranges that were used by him as well.

Q Now, Doctor, if we could go to page 9. You had indicated that she had demonstrated an abnormal IgG2 and IgG4. Was that it?

A That's right.

Q Doctor, are these numbers the numbers that were reported in Michelle's records?

A I think the --

Q I'm sorry. Page 8.

A Thank you.

SPECIAL MASTER HASTINGS: Page 8.

THE WITNESS: Yes. These are just the immunoglobulin subclasses, and I think we've already discussed these.

These are the abnormally elevated IgG2s and IgG4s producing the skewed TH1/TH2 ratio, which Dr. Kennedy has already described yesterday.

BY MS. CHIN-CAPLAN:

Q Doctor, if somebody had an immune abnormality what would you expect to see clinically when you evaluated that patient?

A If you've got immune dysregulation you can see either one or both. You can see either an increased incidence of immunodeficiency, which would

be manifest by frequent infections. Alternatively you could see an increase in autoimmune diseases, or you could see both.

Q And in Michelle Cedillo's case what did you see?

A She's got clinical manifestations of increased proinflammatory cytokines, which is primarily manifest by her chronic bowel inflammation, which would be considered an autoimmune reaction.

And she also has an overly robust response to the toll-like receptors, and that was primarily seen by her abnormal response to the measles vaccine, as well as by her frequent episodes of just inflammation in general.

I'll point out that not only did she fairly rapidly develop chronic bowel disease, but she also had a very unusual inflammatory reaction to what the orthopod thought was probably a small bone broken in the foot, which resulted in a massive inflammatory response, which according to her mom went from the foot and the ankle clear up to the knee and stayed there for a long time before I think it finally cleared on Remicade.

SPECIAL MASTER HASTINGS: Just to clarify, we were back on Slide 9 the last several answers.

MS. CHIN-CAPLAN: That's correct, Special Master.

BY MS. CHIN-CAPLAN:

Q Now, Doctor, if we move to page 11? Did you review the medical literature on the immunology of autistic children?

A I did, and I would highly recommend the Paul Ashwood summary, which actually was referenced in Dr. Kinsbourne's report, called *The Immune Response in Autism: A New Frontier for Autism Research*, because he does an extremely good job of summarizing what is known about the immune status of autistic children in general.

Q Doctor, in your review of the literature can you describe to the Court the types of immune dysfunction that was reported in the literature?

A Yes. It seemed that most of the reports are explaining that there is abnormalities in the response of the innate immune system to various kinds of stimuli and so kind of a central theme here is that these children seem to have an abnormal and overly reactive inflammatory response.

For example, Jyonouchi has taken proliferal blood mononuclear cells from children with ASD, and she's found that in response to a nonspecific

stimulation, which is LPS, they have abnormal levels of three of the chief proinflammatory cytokines, which is TNFa, 1L1B and IL6.

Vargas was a very informative paper because they looked at the actual histology of different brain sections, and they found that these children actually had, just to make it simple because I've detailed it on this slide, but basically they had abnormal activation of the dendritic cells or the dendritic-like cells that are in the brain resulting in actual inflammation in wide areas of the brain.

Q Doctor, can we just stop there for a minute? You indicated elevation of dendritic cells?

A They're essentially the microglia and the astroglia, which are the equivalent of the fixed dendritic cells.

I'm leaving that to Dr. Kinsbourne to describe further to you tomorrow if he wishes.

Q What are dendritic cells?

A Oh, sorry. Those are the main cells of the innate immune system, the ones that when an antigen comes into the body that's the first thing that it sees, and they are usually compared to defenders of the wall of a castle.

Dr. Kennedy described yesterday I thought

very concisely how they react in a very instantaneous fashion to try to block the invaders.

Q So this is your immediate response arm of the immune system?

A Yes, and that's called the innate immune system.

Q Thank you. Were there any other articles that reported the immune abnormalities found in autistic children?

A Yes. I had indicated the fourth one, which is that Ashwood, et al., the same fellow who wrote the review, demonstrated that there was elevated CD3 counts in the gut.

Now, that is part of the adaptive immune system, right, which would be the innate immune system kind of picks up the baton and then passes it on to the adaptive immune system, which takes longer to respond, but is much, much more specific.

That indicates that you have not only activation of the innate immune system, but also the adaptive immune system in the gut, and he was primarily looking at children who have chronic bowel disease. He calls it autistic enterocolitis.

Q So, Doctor, if you see elevated CD3s is that an indication that the innate immune system has

already been activated and was unable to clear an infectious agent?

A Yes, it is.

Q And that the adaptive immune system was now up-regulated or stimulated?

A It's stimulated and attempting to clear the virus, yes, because, as I said before, once you have the virus intracellular the antibodies no longer have an ability to go after it. You've got to use the T cells.

Q So what you're indicating is that the persistent infection allows the infection to enter a cell, and at that point that first line defense can't kill the infection?

A It can't kill it very effectively. It's probably going to continue to be stimulated, but it's now passed the baton onto the adaptive immune system. Both of them are going to continue to be active though.

As long as you've got this foreign body or this foreign matter in your body, both of them are going to continue to work.

Q Doctor, were there any other articles that you thought significant when you evaluated the immune abnormalities of autistic children?

A There were a lot of other articles, and I again would refer the Special Masters when they are looking at the report to the Ashwood review, but I did mention that the ASD patients have other aberrant innate immune responses.

Both of the articles are by Jyonouchi. One is specifically 2000, and then one was an update in 2006.

Q Now, Doctor, when you were evaluating Michelle's case did you determine what potential causes of her immune dysfunction could be?

A Yes. I essentially did a differential which is what you do in internal medicine, and that is that you list the problems that you find and then you list -- actually, a classic differential lists the symptoms, and then it lists the possible diseases.

However, if you're trying to identify a potential culprit you will list the diseases and then you can list the possible causes.

Q And did you do that in Michelle's case?

A Yes, I did.

Q Did you come up with potential possible causes?

A Yes. I found that both the thimerosal that she had received in her prior injections before MMR

and the one or two subsequent to MMR were both responsible in part for her dysregulated immune system.

Q And when you made that determination, had you conducted a review of the literature on mercury toxicity?

A Yes, I had.

Q Just taking one step back, Doctor, is mercury contained in thimerosal?

A Yes, it is.

Q Do you know approximately how much mercury is contained in thimerosal?

A Well, I'm going to defer to Dr. Aposhian for most of the mercury stuff, but I do remember from the Ashwood review they said that something like 47 percent of the vaccine was ethyl mercury, but I would rather defer to him for that stuff.

Q Doctor, moving on to page 12 of your slides, when you reviewed the immunotoxicity of mercury in humans what did you find?

A First of all, I was astonished at the number of papers. I mean, when I started printing out the papers, I was almost papered out -- I was papered out -- of my office because there's an extensive list of the types of toxicities of mercury.

I put some of them on this slide, but I think it would be easier if I just kind of described them. It ranges from these poor sea mammals that have been contaminated with mercury in their water and are found to have frequent infections, particularly as I was describing before.

You look for opportunistic infections; that is, we all have bacteria and virus in us, and a large number of those never cause any problem. When you have something wrong with your immune system, all of a sudden you start getting these opportunistic infections, and that's what these poor animals were getting.

There's been a lot of in vitro studies, so, for example, it inhibits something called the oxidated burst in the neutrophils. Now, the neutrophils are nonspecific parts of the immune system, but they're very valuable because they carry out a seek and destroy mission, and they gobble up a lot of invaders.

The way that they kill their bacteria is by something called an oxidative burst, which kind of blows them up. If that is impaired then you can't eliminate all of these or a lot of these pathogens.

It also causes autoimmune diseases, which is acute glomerulonephritis, and a lupus-like syndrome.

It causes autoreactivity of T cells in humans. It lowers your suppressor cells. There are thousands of articles.

Can I see Slide 13 to see if I went on and on about this a bit? I did. I did go on a bit about this.

Q Are we now on page 13 of your slides?

A We are on 13, and essentially what I'm doing is just trying to list some of the more profound immune dysfunctions that we found here.

Can I have the next one, 14?

Q Fourteen?

A Fourteen. Right. Essentially mercury in whatever its form, and again I'm going to defer to Dr. Aposhian because he will go on and on about the different forms of mercury, but whether it be inorganic mercury, methyl mercury, ethyl mercury, it had multiple roles in disturbing the immune system.

The immune system, I should say we always talk about the immune system as warriors or an army, and that's kind of what its function is. I mean, it's not something like the pancreas where if you're a pancreatic cell you kiss the wife and you go into work every day and you kind of pump out the insulin. These components of the immune system are responsible for

defending against invaders on multiple fronts, and that's what mercury does.

The difficulty that I had when I was reviewing these things is dose. In many of these studies you don't know what the dose was. I mean, how do you know what the dose that a sea otter was exposed to in the seawater?

Although you may know the dose in the in vitro studies, in some cases they were at pretty high doses because if you just want to show that in fact you're getting some kind of a reaction, you know, you chuck in a pretty high dose.

That's the reason why I, and I think the whole field, have been particularly helped by two recent publications, which probably are on 15 if I can have that next slide.

Q Doctor, before we go to 15, in your review of the literature did you notice that mercury affects or causes the full expiration of autoreactive T cells in humans that's on page 14?

A It induces the differentiation of autoreactive T cells, and it is also toxic to the regulatory T cells, which we used to call suppressor T cells. We're not allowed to do that anymore. We can only call them T regulatory cells.

The result is the same, which is that once you induce an abnormal autoimmune response that the body would like to stamp on very rapidly, you have lost the important cell population that allows you to do the stamping, or at least you have disabled it. Those are the T suppressor cells.

Q So would it be fair to state that mercury in any of the forms, methyl, ethyl, inorganic, has a widespread effect on the immune system?

A Yes. As far as actually discussing specifically the type of mercury, I certainly intend to defer to Dr. Aposhian, but, yes, it has wide toxicity to the immune system.

Q So, Doctor, just to summarize for the Court, what conclusions can be drawn about how mercury affects the immune system?

A Mercury in general produces immune dysregulation. It itself is a Hapten, so in other words it can form an intermediate, which then can bind to self-proteins. Once it binds to self-proteins, those self-proteins become immunogenic when they shouldn't be.

It can produce autoantibodies that will react against it. Those autoantibodies can produce all sorts of havoc, including immune complexes and

vasculitis. A vasculitis is an inflammation of the vessels, which is often seen in systemic lupus erythematosus that can be caused by mercury exposure.

I've already described the apoptotic. Let me just tell you what apoptotic is.

Q Yes, please.

A Apoptotic is a programmed cell death, and the deal is that if you have a cell that dies by a necrosis that's an extremely inefficient and a dangerous type of death because it results in scarring, and the insides of the cell are just kind of dumped out in a fairly unregulated fashion, as opposed to apoptosis where it's programmed cell death and the cell is given a death signal and the cell squishes up in a very nice, neat little piece that then can be easily eliminated so it doesn't lead to scarring.

However, it's a main way of killing cells, and in this case you're killing cells that you really don't want to kill, and then finally it induces the differentiation of the autoreactive T cells and, as I've already described, that's particularly dangerous when you are also disabling the function of the regulatory cells that are supposed to sit on them and squash them.

Q Now, Doctor, you indicated earlier that

there was an issue of the dosage that could potentially cause harm.

When you reviewed the literature, were there articles that indicated the amount of mercury that it could take to affect the immune system?

A Finally, yes. There has been at least two articles, and to try to avoid overwhelming the Court I'm trying just to focus on two of them, but there have been more than that. They have concluded dendritic cells are the most sensitive part of the immune system.

Q Again, Doctor, what are dendritic cells?

A Dendritic cells are part of the innate immune system. They are the first defenders of the castle, and when they're triggered they release proinflammatory cytokines so that they can call in all of the other cells from the immune system to start defending themselves.

For example, if you've got your warriors around the outside of the castle they're already armed, but as soon as they find that there is an invader coming in they will not only start to kill the invader, but they'll also send signals out to pull in all of their buddies.

That's the reason that, for example, if you

have a skin test you'll often have a bump. That bump is composed of a lot of cells, a lot of lymphocytes, that have come from other parts of the body and are trying to defend against that invader because your body thinks, I guess, that the skin test that you've put on is an active invader.

Q So this is the first response system, for want of simple term?

A Thank you. I see, yes. It's the first response system, and it's the most sensitive.

If you can't get proper dendritic cells it impairs your ability to come up with cells of the adaptive immune system as well, which are very highly specific and the ones that are going to carry you through long term.

Q So, Doctor, this first response system is affected by mercury, and when the first response system is affected the signaling to the other portion of the immune system is affected as well?

A That's right.

SPECIAL MASTER HASTINGS: I would note again we've moved to Slide 16, I believe. Go ahead.

BY MS. CHIN-CAPLAN:

Q Doctor, you indicated that there were two primary articles that you considered. Could you

kindly describe to the Court these two articles that you considered?

A Yes. Both of them found that the dendritic cells are the most sensitive part of the immune system, and Goth, et al. and Agrawal, et al., and, by the way, Agrawal is actually Gupta because the senior person on that is Gupta.

Both of those studies showed that the range of about 25 micrograms, 20 micrograms, of thimerosal in vitro caused an abnormal IL6 secretion. One of them used murine dendritic cells. One of them used human dendritic cells.

They postulate and they tested different reasons that occurred, and they come up with different reasons. It's certainly not inconceivable or illogical to think that both of those are active.

In other words, you don't have to have just one mechanism by which you're inducing this, but the interesting thing is that both of them are looking at IL6, and both of them are finding that there is abnormal levels of IL6 that is being produced.

Both of them point out in their discussion that this is a level that is much, much lower than the thimerosal that had been given prior to vaccination and at a level that is above that that would be

expected to be given in a single injection.

Q Just to be perfectly clear, Doctor, are you saying that these two articles utilized doses that were less than that seen in pediatric immunization?

A Yes. They were at least at the same level.

Q And at that level they were observing harm to the immune system?

A They were.

Q The cellular portions of the immune system?

A Yes.

Q Doctor, when you looked at Michelle's medical records did you evaluate the vaccines that she received?

A Yes, I did.

Q And on page 17 of your presentation does this indicate the amount of ethyl mercury exposure for Michelle Cedillo?

A It does, and it also gives the age at which she was exposed.

Q Doctor, this chart indicates thimerosal exposure. Do you mean ethyl mercury exposure?

A I think I mean thimerosal, which is of course ethyl mercury.

MS. CHIN-CAPLAN: Just one minute, Special Master.

BY MS. CHIN-CAPLAN:

Q We'll just move on.

A Go ahead.

Q Doctor, could you just kindly go through this chart and tell the Court how much mercury Michelle received?

A Yes. Let's specifically look at the mercury that she received before the MMR because that very dramatic and very colorful demonstration of an aberrant immune system really was manifest at the time that she received her MMR, so let's look at what happened to her.

Let's look at her body burden before. As you can see, she's gotten, let's see, 75, so she's gotten more than 100. I'm going to have to calculate. Let's see.

Q So on day one of her life, which is her birth date, she received how much?

A 12.5 micrograms.

Q And at approximately one month how much did she receive?

A Another 12.5, so now you've got 25 micrograms.

Q Right. And at two months of age?

A She got another 25 micrograms, so now we're

up to 50.

Q Okay. And at four months of age?

A She's got another 25 micrograms, so we're now up to 75.

Q And at seven months of age how much did she receive?

A She receives a total of 37.5 micrograms, so now we're over 100.

Q And after this date does she receive any other immunizations?

A Yes. Three months after her MMR she received at least one shot containing 25 micrograms, and I'm told by you that they were unable to document whether or not she truly received another 25 micrograms.

Q That's correct. Doctor, before that least thimerosal-containing vaccine, did Michelle receive an MMR immunization?

A She did. She received an MMR three months before the last thimerosal-containing vaccine.

Q Okay. Doctor, moving on to page 18 of your slides. Could you tell the Court what this represents?

A Yes. I am giving the Court the site of a castle, and the reason that I'm doing that is not only

to underlie the importance of the innate immune system and explain what it's doing, but it's also because I think you'll probably see it at a lot of presentations, because I'm seeing it more and more, this symbol, being used at different presentations.

And essentially, where do dendritic cells live? Well, they live at the places where you are going to get invasion by pathogens. So therefore, they live in the form of the Langerhans cells of the skin, because you always get cuts with potential invasion. You are going to have them lining your lungs, because you are going to breath in bugs. You are going to have them lining your gut because you are going to be eating bugs. And so, those are the main places that you are going to look for.

You are also going to see them in the liver in the form of Kupffer cells. These are all just, they are dendritic cells that ultimately have become fixed and so we name them different things because the old-timey pathologists didn't really know where they came from.

And so here you've got your fortress of the castle and you've got all your guys who are standing there with their spears ready to, number one, kill the invading organisms, and number two, call in for their

buddies to help them. And again, that was described, I though, very nicely yesterday by Dr. Kennedy.

Q Is this your thinking or this accepted within your field right now?

A It's accepted in the field. That's why I mention that I am seeing this analogy more and more at meetings. It seems like everybody comes up with a new castle.

Q Now, Doctor, as we move on to page 19 of your slides, what does this represent?

A These slides, it's a lecture series that's given by Dr. Abbas. There is a meeting called FOCIS, Federation of Clinical Immunology Societies, and he usually gives this lecture right before the society, and he always has nice pictures.

So this describes in the first panel, you've got a bug that's adhering to the epithelium. Now, of course, that's not relative in the case of the measles vaccination because it's going to be injected, so let's look to the next panel. It's injected, and this little fellow here who has a lot of tendrils represents the dendritic cells. And the red dots are going to represent the measles vaccine virus entering the cell.

It's going to be bound to and phagocytized

by the dendritic cell. The dendritic cell then is going to come loose and it's going to go into the lymph node. And at the lymph node, it is now going to try to pass the baton on to the adaptive immune system, and I mentioned in the legend for the slide the fact that this is one of the places where thimerosal has been shown to be toxic.

Q And does this process continue on, Doctor?

A It does, and I've got several more pretty slides.

Q So if we go to page 20?

A So this shows that the dendritic cell has moved to the lymph node, and then it's presenting the processed antigen to now the adaptive immune system. Now it's trying to pass its baton on to those T cells. Remember I said that they found CD3s in the gut of inflamed bowels of children who have autistic enterocolitis? Well, that's what those things are. And the thimerosal, or actually, in this case, I think it's mercury in one of its forms or another, has been shown to show apoptosis of T cells.

Q And Doctor, on page 21, what do these pictures represent?

A I just put in some pretty pictures of dendritic cells, and the one I like the best is on the

right-hand panel on the middle portion, which is showing you the dendritic cells as they exist with all of their folds. You can imagine that you want to maximize the surface area of a dendritic cell because what it needs to do is capture antigen, and one of the places it's going to capture the antigen is on its surface.

Q Thank you. Doctor, I just want to move back to page 17 of your presentation, and I am going to refer you to Respondent's Exhibit No. ii. And I am going to ask you to look at Table C on ii. So Doctor, on Table C of ii, as compared to your chart on page --

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, can you wait just a minute for us to get it? Is that the IOM report?

MS. CHIN-CAPLAN: Yes. Appendix C of the IOM report, thimerosal containing vaccines. We are looking at Table C-1. There is a slight correction here. It is my error.

SPECIAL MASTER HASTINGS: Just one minute. Is there a page number?

MS. CHIN-CAPLAN: It is page 17.

SPECIAL MASTER HASTINGS: Okay, I'm sorry.

SPECIAL MASTER VOWELL: It's not slide ii?

MS. CHIN-CAPLAN: No, it's slide 17, and I

have pulled out Respondent's Exhibit No. ii.

SPECIAL MASTER HASTINGS: Right. I am asking for a page number of Exhibit No. ii.

MS. CHIN-CAPLAN: Exhibit No. ii, it's just Table C-1 at the back, and there doesn't seem to be a page number.

SPECIAL MASTER HASTINGS: All right. Page 127, I'm told.

MS. CHIN-CAPLAN: Right, and I just wanted to correct an error that was made by me.

BY MS. CHIN-CAPLAN:

Q Doctor, when we look at your chart that you provided on Michelle Cedillo's immunizations, it indicates thimerosal for Michelle Cedillo, is that correct?

A That's right.

Q And on the far right-hand column it says, 'thimerosal amount.' Is that correct?

A Yes, it does.

Q And Doctor, when you compare it to Table C-1 of Respondent's Exhibit No. ii, would the proper term be 'mercury,' as opposed to 'thimerosal'?

A Well, let me see. They are saying 'percent thimerosal concentration' and then they are saying 'mercury in micrograms.'

Q And Doctor, when we referred to the micrograms in your chart on page 17, does that refer to mercury?

A I thought that that referred -- I'm sorry. At the break, maybe I will check, because I was given the information that that was thimerosal.

Q Correct, but according to the IOM chart?

A According to the IOM chart, yes, but you are looking at DPT, which is 25 micrograms, right? Okay, so here is your Hepatitis B, and so it is listing 12.5 micrograms, and its title says 'mercury' instead of 'thimerosal.'

Q Thank you, Doctor. So, moving on, Doctor --

SPECIAL MASTER HASTINGS: So let me make sure that I understand what the point of that discussion was. On slide 17, Dr. Byers, you have in your right-hand category, it says 'thimerosal amount.'

THE WITNESS: That's right.

SPECIAL MASTER HASTINGS: And after looking at the IOM table that you were just talking about, are you saying that actually -- let's take the first entry. On August 31, '94, Michelle got a Hepatitis B vaccination. You are saying that she actually got 12.5 micrograms of mercury as part of that vaccination, rather than 12.5 micrograms of

thimerosal?

THE WITNESS: That's apparently what the IOM is saying, and I think what I would like to do is to defer to Dr. Aposhian for the actual chemical structure of the compound, because I have not read this paper for quite a while.

SPECIAL MASTER HASTINGS: Okay, fine.

Go ahead, Ms. Chin-Caplan.

MS. CHIN-CAPLAN: Thank you.

BY MS. CHIN-CAPLAN:

Q Dr. Byers, moving on with your testimony here, we are now on page 22. Would you tell us what this slide represents?

A Yes, this is just a continuation of the little slide presentation I put together, indicating the fact that mercury is involved at multiple places in the immune system. This is showing, again, the innate immune system with a macrophage dendritic cell containing a phagocytosed microbe producing both cytokine production and beginning to impact on the adaptive immune system.

Q So this is a depiction of your immediate response system?

A Yes, it is.

Q And Doctor, will you move on to page 23?

A This slide was actually also utilized by Dr. Kennedy yesterday. It points out though that the ability to clear invading microbes is impeded by damaged macrophages or dendritic cells, as would have been damaged by mercury.

Q And Doctor, what does page 24 represent?

A That represents the regulatory cells. Remember, I was saying earlier that mercury actually stimulates autoreactive T cells, but normally those autoreactive T cells would be squashed by the regulatory T cells. However, mercury also damages the regulatory T cells.

Q So are you describing damage to all aspects of the immune system?

A Yes, and probably by, again, different chemical parts, different chemical presentations of mercury.

Q And Doctor, if you had to summarize for the Court the effect that mercury has on the immune system, what would you say?

A I would say that the most important thing that we should now be concerned with is the effect of thimerosal on the ability of dendritic cells to behave in a normal fashion so that they can clear viruses.

Q And more specifically, on page 25 of your

presentation, do you detail how it affects certain elements of the immune system?

A Yes, it impacts on the secretion of LPS, of the different proinflammatory cytokines, and the reason that is important is it means that it is going to impair the ability of the dendritic cells to stimulate the adaptive immune system, which is, long-term, the way that you are going to have to get rid of and clear the virus. It is also inducing elevated TH2s, which are going then to inhibit the very cells that are supposed to be able to do this in the adaptive immune system.

It's going to alter the IL6 secretion. That was shown by the Goth et al. paper. And it's also going to produce apoptosis in T cells. This is not one of the two key papers that I pulled out, but it basically is saying that it is producing apoptosis by oxidative stress and depletion of the glutathione within the cells, which I think Agrawal also showed.

Q And Doctor, as a result of this ability for mercury to cause immune dysfunction, what could happen to an individual?

A The individual could have the ability to normally clear viruses and bacteria from their system impaired, which would then result in a chronic low-

grade inflammatory response that was dysregulated.

Q And what happens when a chronic low-grade inflammatory response occurs?

A It produces autoimmune disease. In fact, the new name for autoimmune disease is, let's see, immune- mediated inflammatory disorder, to underlie the fact that inflammation is a key hallmark of many of these autoimmune diseases, and many of them are initiated by dysregulation of the innate immune system.

Q And Doctor, what causes the inflammation?

A The inflammation is caused by cytokines that are released. And the cytokines are released from both the innate and the adaptive immune system. They just keep churning around because they can't get rid of the invader.

Q Doctor, in your opinion, if there is a dysfunctional immune system when a child is administered an MMR immunization, will that affect the ability of the body to clear the measles virus?

A Yes, it can.

Q And Doctor, in your opinion, would that be a substantial contributing factor to the persistence of the measles virus?

A Yes, it would.

Q Now, Doctor, if we move on to page 27, what is this?

A I think you need to flip back to 26.

Q Okay.

A So, because I think people throw around the idea of cytokines, and cytokines are just proteins, and they are proteins that are produced both by the innate and by the adaptive immune system, and they can be toxic to multiple organs, and they are released immediately on interaction with the dendritic cells. Now you can go to the next slide.

Q Thank you.

A Well, it's a pretty slide.

Q Very pretty. Could you kindly explain to the Court what this slide represents?

A Yes. It represents a dendritic cell. The little 'pDC' at the upper right stands for plasma dendritic cell. And it is mapping out the path by which activation of the pathogen results in secretion of proinflammatory cytokines. And the thing to know about this is that there are only about 10 different specificities when you are kind of entering in, and I've given you the one that binds and is stimulated by single-stranded RNA, which would be the measles virus. And then you have these complicated pathways, and

there is at least two of them, but the main thing is that they all result in the secretion of pretty much the same thing, which is the proinflammatory cytokines.

So you've got a bunch of different things coming at you. The immune system, the innate immune system is segregating them into 10 different broad categories, and then those 10 different broad categories are activating the -- they are called toll-like receptors in the innate immune system, and the end result of it is pretty much similar; it is the secretion of proinflammatory cytokines, which is then ultimately going to recruit other warriors to help you eliminate your virus.

Q So Doctor, to be perfectly clear here, if a child has an immune system that was affected by mercury, and then received an immunization with measles-containing virus, would that child have difficulty clearing that virus?

A The child could. Now, obviously, everybody doesn't, because lots of people get mercury-containing vaccines and as far as we know, they clear them fine.

Q And if that child had difficulty clearing the virus, what would you expect to see in that individual?

A You would see persistent measles virus which would continue to produce an inflammatory response and ultimately an autoimmune condition, which could be specific, it could be nonspecific, because the body is still trying to get rid of the virus.

Q When you have an inflammatory response, are there certain elements of the immune system that respond?

A It's both. It's both the innate immune system and the adaptive immune system. They are both secreting proinflammatory cytokines.

Q Okay, and Doctor, are those proinflammatory cytokines restricted to a particular spot in the body?

A No. To continue your analogy, they are going to be primarily focused in the places where the virus likes to live, and as Dr. Kennedy described yesterday, two of those places are the gut and the brain. So it's not surprising that we have found measles virus in the inflamed gut.

Q So Doctor, if there is a localized infection, inflammatory response, would that inflammatory response move systemically?

A Yes. The most well-known pathology of that, of a systemic, chronic infection is, not only do you have inflammation and dysfunction of the organ where

the battle is going on, but you also have systemic release of cytokines, and those very famously go to the brain and cause brain pathology. One of them, TNFα, destroys or affects the blood-brain barrier, and that really allows a lot of the cytokines to move into the brain.

So that means a systemic inflammation can affect multiple parts of the body, including the brain.

And if it affects the blood-brain barrier, what happens to the blood-brain barrier?

A For cytokines particularly, they can more easily cross. Additionally, however, you have activated lymphocytes that have access to the brain, and a neuroimmunologist would tell you that for an activated lymphocyte, there really is no blood-brain barrier.

Q So that means that the cytokines are able to freely move across the blood-brain barrier?

A Well, they can move more freely than other molecules would. And from slide 29, this can include IL1, IL2, and TNFα. And they can be passively transported or can be actively transported, and I think when I made that slide, when I said actively transported, I meant that they are coming from

activated lymphocytes, which, as I say, can easily wiggle through the blood-brain barrier.

Q And Doctor, what happens when cytokines affect the CNS?

A There is a lot of CNS pathology. IL1β induces local inflammation in the brain, and I have given --

SPECIAL MASTER HASTINGS: Now you are reading from slide 30?

THE WITNESS: Slide 30, yes. IL1β induces local inflammation in the brain, it induces gamma receptor function in the neurons. What I want you to take away from this is that it just, it produces a lot of CNS pathology. One of the probably the most important ones here is nitric oxide, which is produced by macrophages and can actually directly biochemically affect the function of the electrical transmission of the neurons, and that, among other, has been heavily implicated in the flares that you get with multiple sclerosis.

Q And Doctor, are cytokines also administered as a drug?

A Oh, yes. We learned to produce cytokines in a commercial formulation some years ago, and as a matter of fact, you might be amused to know that one

of the first ones to be administered was TNFα. TNFα used to be called the old cachectin, which was the reason that people lost weight when they developed various cancers, particularly ovarian cancer, and it also can produce apoptosis.

So some bright sparks decided that they would purify TNFα and give it to see if they can cure cancer, and the effects were absolutely disastrous, so therefore, TNFα has never been marketed. However, some of the other cytokines are standardly marketed, and they all have black box warnings.

Q What does that mean?

SPECIAL MASTER HASTINGS: Now we are slide 31, correct?

MS. CHIN-CAPLAN: That's correct, Special Master.

THE WITNESS: I'm not being very good about giving you the -- sorry about the page number. I'll try to be better.

A black box warning is, essentially, one where the FDA is so concerned about it so that the first thing you see when you open your PDR is this black box. It's the main thing that the doctors need to worry about. So for example, I am giving you IL2. IL2 is one of the main cytokines released by T cells,

and it's a cause of fever. And if I remember rightly, it has been used I think to treat renal cell carcinoma some time ago.

And the black box warning says it must be withheld in patients with lethargy or somnolence, in other words, people who are drowsy and not really very with it mentally, because if you don't, it'll result in a coma, which is obviously a very marked CNS effect. Additionally, they say, change in mental status, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation and coma may result, and it may cause seizures.

I gave you this slide to demonstrate how a peripheral inflammation or peripheral injection of these cytokines result in CNS dysfunction.

Q And are there other cytokines that can be administered?

A Yes, I pulled out interferon-α --

Q Page 32.

A -- which is on page 32, which is also secreted by various members of both the adaptive and the innate immune system. It causes or aggravates fatal or a life-threatening neuropsychiatric autoimmune ischemic and infectious disorders. It produces depression, psychosis, nervousness, anxiety,

emotional lability and agitation, and 26% of the patients reported mild to moderate depression, and that was the most common reason for stopping the drug.

Q And Doctor, is there another cytokine?

A There's a bunch of other cytokines. Here's on page 33, IFN-β, which increases depression and suicide, seizures, and the best demonstration that these symptoms are caused by the administration of the cytokine is that the CNS problems resolve when the treatment is stopped.

Q So Doctor, would it be fair to state that there is a correlation between cytokines that normally occur in the body and those that are administered peripherally?

A Yes.

Q Would they have the same effect?

A One would expect them to have the same effect, yes.

Q Okay, and Doctor, do cytokines have an effect on the neurological system?

A Yes, I've already described that they have an effect on the neurologic system, but on slide 34, I wanted to give the reason, and the reason is that there is a very close interaction between the immune system and the neurologic system. The immune system

produces cytokines, which are active on the neurologic system, and the reverse happens, which is that the neurologic system produces cytokines that in turn interact with the immune system.

And I would once again refer you to the Paul Ashwood review, because he has a very nice description of the interaction between those, so that when you guys are getting ready to write your opinion up, you might use that as a reference.

Q So they cross-talk? They talk to each other?

A Yes, they chit chat. So the neurons have the cytokine receptors from the immune system, and IL1, IL6 and TNFα induce the production of nerve growth factors. TNFα and IFN-γ interact with the neuronal adhesion molecule responsible for neuronal development, synaptogenesis and regeneration. All of those things I am going to leave to Dr. Kinsbourne to interpret tomorrow, but I felt it was my responsibility to describe what these interactions are.

Now I am on 35. IL2, look at the third bullet. Again, we've got IL2 receptors in one of the important cell layers of the hippocampus. We've got IL2 contributing to regulation of neurotransmission in

that same area. It can provoke schizophrenia-like symptoms in humans as one of its side effects.

Q When you say neurotransmission, are you talking about the way in which they talk, is that it?

A I'm talking about the way that neurons talk to each other.

Q So the signal that they send?

A Yes.

Q And IL2, which is a cytokine, affects the way the signal is sent from the neurons to the immune system, and vice versa?

A Yes, it can do that. Nitric oxide is better known to do that.

Q And are there other proinflammatory cytokines that affect the neurotransmitters?

A Yes. I've described the disastrous clinical trials that we did with TNFα, so we don't have a black box in the PDR to look for that. However, we do have other data indicating that TNFα will, for example, its chronic release will inactivate catecholamine secretion. It can play an important role in demyelination in multiple sclerosis, and in my review of the literature, it was the main culprit in impairing the blood-brain barrier.

Q And Doctor, when we move on to page 37, is

IL6 a proinflammatory cytokine as well?

A It is. IL6 is actually turning out to be the hot topic of the month because we have now just developed a monoclonal antibody against IL6 which is proving to be highly effective against a variety of autoimmune diseases. It is, again, synthesized by mononuclear cells, by endothelial cells of the vessels, and also by fiberglass, and there are so-called stress receptors for IL6 in the hippocampus, and I put that in because I think Dr. Kinsbourne might have an opinion as to the implications of that, because it's certainly important in cognitive function, and it's abnormal in autistic children.

It's also involved in other neuropathology such as Alzheimer's, because one paper said that there was elevated levels of IL6 found in plaques of Alzheimer's patients.

Q Now, in bullet number 2, you say 'stress receptors.' What are stress receptors?

A Stress receptors are simply receptors that will dysregulate and cause abnormal function of the neurons, and again, I'm going to leave it to Dr. Kinsbourne to decide whether he would like to comment further on that.

Q And the hippocampal dentate gyrus, is that a

portion of the brain that you are referring to?

A Yes, it is.

Q Doctor, moving on to page 38, you have indicated that cytokines can cause inflammation in the brain. Is there a specific area within the brain that the inflammation occurs?

A Yes. This is a quote from the abstract actually of a recent paper called 'Effective Inflammation on the Microglia of the Brain,' and in this case, it was an animal study where they injected LPS. And remember, LPS is one of the main and more powerful stimulants of the toll-like receptors, and so what they are doing is they are administering LPS systemically and then they are seeing if there is an effect on the brain.

And they did find that there was a rapid increase in TNFα in the brain, and the interesting thing is that this remained elevated for 10 months after injection, which was a marked change in the pharmacokinetics of the TNFα in the periphery where in serum it was dying down by about nine hours and in the liver, it was dying down by about a week. And the injection of this activated the microglia and it increased the expression of multiple brain proinflammatory factors.

Again, this is the same theme that I've given you, probably, what you think is too many slides, to basically say that these cytokines, when administered systemically, have an effect on the central nervous system.

Q Doctor, the TNFα, is that it?

A Yes.

Q That's a proinflammatory cytokine?

A Yes, that's the proinflammatory cytokine that Enbrel, which I helped develop, blocks, and it's also the one that Remicade, which is the one that Michelle Cedillo responded to, Remicade also blocks TNFα.

Q That remained elevated for 10 months in the brain?

A That's what they report.

Q And at the same time, by the end of nine hours, the level had decreased in the blood?

A That's what they reported.

Q And the levels had decreased by one week in the liver.

A That's right.

Q So the message here could be that even though you have normal serum levels of proinflammatory cytokines, you could still have inflammation going on

in the brain?

A That is certainly correct, and it's correct for other parts of the body as well. For example, with rheumatoid arthritis, you can have perfectly normal levels of TNFα in the periphery, and yet have very elevated levels of TNFα in the joints.

Q So the peripheral, the blood work that is drawn, is not an accurate reflection of what is going on the brain necessarily?

A It is more accurate to actually take it from the brain, and it's certainly more accurate to take it from the synovial fluid if you have rheumatoid arthritis.

Q Doctor, could you kindly summarize for the Court the facts that we have referred to here?

A Yes. She suffers from immune dysregulation. This is manifest clinically by the abnormal febrile reaction that she had to her MMR vaccination, followed by the inflammatory gut reaction, which was apparent within two weeks after the immunization. According to her mom, as the fever started to drop, then they were actually able to start looking at the first symptoms of the chronic bowel inflammation, and the reason that the body had difficulty in eliminating the thimerosal, or the mercury, from the body is because the

thimerosal had damaged the ability of the immune system to clear the virus, allowing viral persistence. And for this, I am relying upon, in part, Dr. Aposhian's report about the abnormal mercury efflux from autistic patients, as well as the fact that he finds that there is a mercury build-up in the immune system.

Q Doctor, based on your education, training and experience, and your review of the medical literature regarding both thimerosal and measles, do you have an opinion whether the mercury that was contained in Michelle Cedillo's vaccines substantially affected her immune system?

A Yes, I find that the mercury that was given to her in her vaccines leading up to MMR lead to a difficulty in her immune system in eliminating the measles virus from the body.

Q And Doctor, what is the basis of your opinion that immune system was substantially affected by the mercury that was contained in her vaccines?

A The fact that there has been substantial literature indicating that mercury in general damages multiple parts of the immune system, and that the doses of mercury which she was given is capable of damaging at least the dendritic cells.

Q And Doctor, do you have an opinion whether the virus that was found in Michelle's gut tissue from Unigenetics was persisting approximately four years after her immunization with MMR?

A Yes, I have, and I am relying upon the testimony of the two experts who testified yesterday, that in fact that is correct.

Q Doctor, do you have an opinion whether persistent measles virus was the result of her dysregulated immune system?

A Yes, I do. I find that the dysregulated immune system would have impaired the ability to clear the measles vaccine in a normal fashion.

Q And what is the basis for that opinion?

A The basis for that opinion is that it is there, and that we have demonstrated clinically and from laboratory tests that she does and did have a dysregulated immune system.

Q And Doctor, do you have an opinion whether persistent measles virus can cause CNS dysfunction?

A My opinion is that persistent measles virus which results in inflammation, particularly bowel inflammation, can cause CNS dysfunction, and I will point out that bowel inflammation is absolutely notorious for causing CNS dysfunction ranging from

Crohn's disease to ulcerative colitis to certainly celiac disease.

Q And Doctor, do you believe that more probably than not, that the mercury contained in Michelle's vaccines substantially harmed her immune system?

A Yes, I do.

Q And do you believe more probably than not that the measles virus in her gut was a persistent virus?

A Yes, I do.

Q Do you have an opinion whether or not that persistent measles virus was a result of her dysregulated immune system?

A Yes, I do.

Q And do you have an opinion, more probably than not, whether persistence of that measles virus caused CNS dysfunction?

A Yes, it caused inflammation, and inflammation is certainly associated with CNS dysfunction in a wide variety of experimental models as well as humans.

MS. CHIN-CAPLAN: Thank you, Doctor.

SPECIAL MASTER HASTINGS: Why don't we take our morning break at this point? I have 10:44. We'll

start back promptly at 11:00 a.m.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: For those at home, we are ready to go back on the record.

Ms. Chin-Caplan, have we lost our witness?

While we are searching for the witness, let me remind all counsel, especially those at the counsel tables, anywhere where you have a microphone, on this phone conference system, we start at 8:35 or sometime in the morning, turn it on, and these microphones are live all day. They are live during the breaks, including the ones at your tables, the ones up here on the bench, so that you can act accordingly. I just wanted to make you aware of this. For technical reasons, the phone conference stays on all day until we adjourn for the rest of the day, so be so advised.

Are there any matters that we need to talk about today, counsel?

MR. MATANOSKI: Not from the government, sir.

MS. CHIN-CAPLAN: Special Master, I am still intending to call Dr. Kinsbourne tomorrow, and even if we finished early today, I would like to adjourn early and start first thing in the morning. And I expect to be completed by tomorrow.

SPECIAL MASTER HASTINGS: I understand.

All right, I see we have a sighting of Dr. Byers, and she is proceeding towards the witness stand now.

Dr. Byers, you are of course still under oath, so with that, Mr. Matanoski, do you have any questions for this witness?

MR. MATANOSKI: Yes, sir. Thank you

SPECIAL MASTER HASTINGS: Please go ahead.

CROSS-EXAMINATION

BY MR. MATANOSKI:

Q Good morning, Dr. Byers.

A Good morning.

Q I know we were just looking for you to sit there at the witness stand. I hope that it wasn't because I was about to speak to you that we couldn't find you.

A Well, there was certainly a moment of terror there.

(Laughter.)

BY MR. MATANOSKI:

Q Doctor, you were here during testimony yesterday, correct?

A Yes, I was.

Q And you got to hear Dr. Kennedy speak?

A Yes, I did.

Q Anything that he said yesterday that you disagree with?

A As I sit here right now, I cannot remember anything that he said that I disagreed with.

Q Could you lay out for me step by step what your theory of causation is in this case?

A Yes. My opinion as to causation is the child had a -- one has to say that simply because one is autistic, one has a compromised --

Q Actually, maybe if you would just go through it step by step, I'm sorry.

A I am doing that. One has to say that genetically, an autistic child has an immune system that is innately prone to being damaged, and it appears that the main place that it is going to be damaged is by an aberrant reaction to environmental stimuli. And in the case of Michelle Cedillo, she was partially compromised by the thimerosal that she received, producing a burden of mercury in her body, which resided in the cells of the immune system, or the organs of the immune system, and for all of that, I am relying upon Dr. Aposhian.

And however, she escaped unscathed from any symptoms until she received her MMR vaccination. When

she received the MMR, the time at which she developed a fever was not unusual. However, the extent of the fever was very unusual. Mother reports that it went up to 106, and Mom became very concerned about it. From the records, it appears to have waxed and waned slightly over the next two weeks, and at the end of that time, the continued fever was confirmed at a clinic visit, at which time I think it was 100.6. So it's still a significant fever.

As it resolved, she then became symptomatic with inflammatory bowel disease. She was, shortly after that, let's see, probably -- I don't have the -- I think at age 3, or she was vaccinated at age 1 and a half. It was a pretty short time after that that she actually had the immune evaluation by Dr. Gupta and was found to have laboratory abnormalities, although not the ones he had expected.

She then was found to have inflammatory bowel disease, and that has basically continued throughout her life, and she was then later demonstrated to have persistent measles virus in the gut. And so it is my opinion that the clearance of the measles virus was impaired by the body burden of mercury. However, the trigger for the autoimmune reactions which have now plagued her for the rest of

her life were triggered by the MMR, which resided for an unusually long period in her body and could not be cleared.

Q So that's your opinion?

A Yes.

Q Starting with the first premise of that, so genetically, there has to be a genetic component to this, that someone is genetically susceptible to immune dysregulation as part of your theory?

A The literature would indicate that. The literature would indicate that not only do you have genetic abnormalities that are found in a substantial number of these children, but there is an awful lot of studies on their immune system indicating that the immune system is abnormal.

Q Okay, so it's a genetic abnormality to make the immune system susceptible to being abnormal, or to make the immune system abnormal?

A That is at least one of the results of the genetic abnormality, and the only one that I am responsible for.

Q And that's part of your theory of causation here?

A That's part of my opinion, yes.

Q And you also mention that there was receipt

of thimerosal-containing vaccine. Was that a necessary component of your theory?

A In Michelle Cedillo, it's got to be. It does not necessarily have to be a component in other autistic children, because I believe each one must be evaluated separately.

Q Okay, so you don't need thimerosal-containing vaccines, then, to reach an opinion that an autistic child who received MMR, I suppose, had it because of the MMR vaccine, had their autism because of that?

A As just a broad statement, I would not refuse to evaluate an autistic child who had received MMR but had not received thimerosal-containing vaccines, if you could find them.

Q I'm not talking about whether you would refuse to treat them.

A No, I wasn't either.

Q I'm trying to figure out -- well, that's how you framed your answer. I'm trying to figure out what your theory is and how it will apply in a broad variety of situations so I can know when you would conclude that the case before you was a case of autism prompted by vaccination. Now, we got to the second step, thimerosal-containing vaccines, and though

that's true in this case that the child received thimerosal-containing vaccines, that's not necessary for your opinion. Is that right?

A No, that is incorrect. My opinion is case-specific, and my opinion is based on the fact that the evaluation of Michelle Cedillo includes the fact that she received substantial doses of thimerosal and then received measles virus which was found to be retained in her gut.

Q So if I were to give you a case and I took out the thimerosal, would your opinion be the same? Every single fact of that case is the same as in this case, except there is no receipt of thimerosal-containing vaccines proven.

A I'm sorry, I cannot give you that broad an answer. The best answer I can tell you is that if there was an autistic child who had demonstrated persistent measles and had not received thimerosal, I would certainly think that it is worthwhile evaluating that child clinically again. People are just not cookie cutters.

Q I need to find out whether your opinion, a sine qua non for your opinion is receipt of thimerosal-containing vaccines. So you assume the facts are exactly the same as this case, and you take

out, the only fact that's different is that you do not have evidence of receipt of thimerosal-containing vaccines. Is your opinion the same?

A I'm sorry, I can't say that. I would have to evaluate each individual child separately.

Q I'm giving you the facts. This is a case for you to evaluate. The facts are exactly the ones you are familiar with in this case, except you can take out the page of your slide presentation with thimerosal-containing vaccines in it, and assume that's the fact pattern before you. Now you are asked to evaluate that case. What is your opinion?

A I would say I have to evaluate the case individually. I would not refuse to consider the contribution of MMR in the absence of thimerosal.

Q Do you have an opinion in that case as to whether or not the child's MMR vaccination would cause their subsequent ASD?

A I would be willing to evaluate the child to see if the MMR vaccination, what the manifestations of the MMR vaccination might be.

Q Doctor, I am giving you the exact fact pattern. I am asking you to evaluate it. You said you are willing to do that. Please do it.

A I'm sorry. I think you just, you can't do

that. There is going to be differences. There is going to be differences --

Q There is no differences, Doctor. It is this fact pattern, except there is no thimerosal-containing vaccines. Can you render an opinion or not?

A I could not render an opinion without individually looking at the report.

Q I am telling you what the facts are, Doctor. You have already been through, you have a clinical history in your slide presentation.

A I'm not willing to -- go ahead.

MS. CHIN-CAPLAN: Is Dr. Byers to assume that the child has a dysregulated immune system?

MR. MATANOSKI: It's every fact of this case, except the receipt of thimerosal-containing vaccine.

THE WITNESS: The child --

BY MR. MATANOSKI:

Q These judges are going to have to decide cases, and this is supposed to be a general causation as well as a specific causation. Now, you have before you a fact pattern that you can use to render some opinions. I am asking you to change one fact, and that is receipt of the thimerosal-containing vaccines. The purpose of that question is to find out whether

or not receipt of thimerosal-containing vaccines is critical to your opinion.

A It is not.

Q Next part of your theory --

SPECIAL MASTER HASTINGS: The answer was it is not?

THE WITNESS: That's correct. I would not refuse to evaluate a child who is autistic and who had not received thimerosal but had shown that she had persistent measles virus. I think the Special Master wants to say --

SPECIAL MASTER VOWELL: I don't understand how you are using the word 'evaluate,' Dr. Byers. We are talking about making a causation determination here, and 'evaluate' to me says, I'm going to look at the child, I am going to look at her records, and then I am going to make some decision based on that, but it doesn't tell me what you think about causation. I don't want us to play semantics, I want to understand how you are using that word. So what does 'evaluate' mean to you?

THE WITNESS: It means that, in this case, thimerosal and MMR are contributors to her condition, but it means that I, myself, would not be willing to do a cookie cutter. I gather if you have somebody who

is named Michelle Cedillo, who had received all of the vaccinations but did not have thimerosal in it, but that then was vaccinated with the MMR and was found to have only autoimmune disease and chronic bowel inflammation, then I would say that it is certainly very possible that the autism and that the dysfunction was a result of the measles virus, but I still would be very uncomfortable giving you guys an opinion that would allow you to cookie cutter people because there are so many variations in this.

There is variations in the types of autism. Certainly there is variations in the types of the immune dysregulations.

SPECIAL MASTER HASTINGS: I appreciate your discomfort with hypotheticals, although I do want you to understand, we've got 5000 cases. We are hoping to not have 5000 three-week trials. I don't think you want to come here for 5000 three-week trials.

THE WITNESS: I sure don't.

SPECIAL MASTER HASTINGS: So what we are hoping to get here and the whole point of using the test case was to get from the experts some kind of general opinions that could help us evaluate additional cases. Now, if you can't answer it, you can't. I'm just saying that's what we are hoping to

get. Your opinion may be helpful to Michelle Cedillo. If you can't go beyond her case, it won't be helpful to any of the other 5000.

So to the extent you can give us your general thoughts, it would be helpful. I'll leave it at that.

THE WITNESS: Thank you, Special Master. If I need to do what you have just asked me to do, then you might as well let me go home. What I can do is to tell you that one of the cut points that you can use, one of your screenings that you can use is to look at children who have, one of the groups that you can use, is to look at the children that have had thimerosal in the same dose as Michelle Cedillo, because that's about the same dose that kids get, or at least kids got in her day, and look at somebody who has an aberrant reaction to the measles vaccine, clinically, and look at somebody, if that same person then has persistent measles virus in the gut, then you can make a pot and you can put that person in the pot and say, all right, I'm going to send that out for medical evaluation.

Now, I mean, I guess that's not going to give you exactly the clean answer that you want, but you and I are trying to interface between legal,

scientific and medical, and I think we have to come to a match point, a meeting of the minds, and I can at least give you what I just gave you, and I think that should help. I don't know what those 5000 cases look like.

SPECIAL MASTER HASTINGS: All right. Go ahead, Mr. Matanoski.

BY MR. MATANOSKI:

Q So Doctor, do I understand your testimony to be that in the absence of thimerosal-containing vaccines, and the same fact situation are present, you have no opinion?

A That's true. But further, I've given you a more general outline of someone who should be medically evaluated. It's a little more general than you want, but I think it's better than you've got now.

Q So the receipt of thimerosal-containing vaccines, in your view, may or may not be important?

A In this case of Cedillo, it certainly is important.

Q My question is, in your opinion, the receipt of thimerosal-containing vaccines may or may not be important. Is that correct?

A Yes, depending upon other factors of the case, and I've laid down what those are in somebody

who received MMR and thimerosal.

Q Okay. Let's turn to the next factor. Actually, turn to another fact-specific factor. How long after receipt in your view of thimerosal-containing vaccines is it necessary -- what's the range in terms of the difference in time between receipt of the thimerosal-containing vaccines and receipt of MMR vaccines?

A I'm going to rely upon Dr. Aposhian for that. In this case, he tells me that the, I think it was, 5 months, 8 months, something like that, after the last receipt of thimerosal, still produces a significant body burden. I would turn to him for the extension of that range.

Q So you are unable to render an opinion on what the range should be in terms of the time limit between thimerosal-containing vaccines and receipt of MMR, as far as its clinical significance in the development of autistic spectrum disorders?

A I think that's a fair thing to say, yes.

Q You mentioned receipt of thimerosal-containing vaccines and fever thereafter. The fever in this case was seven days, approximately seven days. Is the fever a necessary element after MMR for you to reach a conclusion that autistic spectrum disorder was

caused by that MMR?

A Well, now my opinion is not that autistic spectrum disorder is caused by the MMR.

Q So we don't need the fever as a clinical manifestation after the MMR for you to reach your opinion?

A That is not what I said. May I clarify this?

Q Absolutely.

A The part of your statement that I did not agree with is when you said that MMR causes autistic spectrum disorder.

I do not have the qualifications to be able to say that. That needs a pediatric neurologist. That is the reason that Dr. O'Leary could not say it. That's the reason that Dr. Kennedy could not say it. That's the reason I can't say it.

What I can say is that MMR was associated with an abnormal inflammatory reaction to the virus which then was in part responsible for the chronic bowel disease.

Q Give me a moment. I thought I had understood you to say this morning that it was your opinion that Michelle Cedillo's autistic spectrum disorder was caused by the receipt of her MMR vaccine.

Do I understand your last answer to be that you can't render such an opinion; you need to rely on some other expert?

A Yes, that is correct.

Q Now turning back to the fever, as far as for your part of this opinion is development of fever a necessary clinical symptom after receipt of MMR for you to reach your conclusions about the role of MMR and the subsequent development of autistic spectrum disorders?

A No. The subsequent development of bowel inflammation.

Q Is fever a necessary element, in your opinion, about the subsequent development of bowel disorder?

A I have taken the position, and I've been working in the Vaccine Court for some time, that if there is not some sort of an evidence of inflammation following a temporally reasonable time after a vaccination then my suspicion of the vaccination is significantly decreased, and as a rule of thumb I have used fever.

I can't tell you that another expert might not use something else because basically any evidence of abnormal or unusual cytokine release is indication

of abnormal activation of the innate immune system, which then can trigger an autoimmune disease, but as you sit here looking at this expert in front of you I can tell you that fever in my opinion is generally necessary for me to assume that there is activation of the innate immune system.

Q Okay. So it is important to your opinion about the formation of the cytokine release?

A Yes, it is.

Q In the absence of fever, would you render the same opinion?

A I don't know. Let me give you a hypothetical. Suppose that somebody had gotten a vaccination, and for some reason or another they had not gotten fever, but you had drawn blood and you had demonstrated that there was a very abnormal release of the other proinflammatory cytokines.

Then I think a reasonable expert would have to say I don't know why there's a lack of fever, but look, I've got these other things, and I'm going to include them. As a rule of thumb though, I have said I want to see fever.

Q So for your opinion, fever is a critical element?

A It has been in the past. I may change it

and a different expert may not follow in my footsteps.

Q To reach your opinion, is it necessary, the opinion you've reached in this case, and I understand you aren't going to the ultimate opinion.

I'm sorry. Are you having trouble hearing me, Doctor?

A You have a very low voice.

Q I'm actually having a little trouble keeping my voice. I apologize.

In your opinion, is the development of inflammatory bowel disease necessary for you to reach the conclusion that you have?

I understand that you haven't reached the ultimate conclusion of whether the autism was caused by MMR, but to the extent as far as you're going with your opinion, is development of inflammatory bowel disease necessary to bring MMR into a causative role?

A Yes. In the case of Michelle Cedillo, I am strongly influenced by the fact that she had inflammatory bowel disease with all of its impact on the CNS and that the measles virus was found in the inflamed gut.

Q Okay. Strongly influenced. Is it a necessary element, Doctor?

A If she had no other evidence of

inflammation, including no fever and no reason for an abnormal lack of a fever, then I would have to rethink my opinion as to whether or not any CNS pathology was caused by the measles.

Now, assuming that I can't find any measles any place else in the body and I have no evidence that the measles was abnormally retained.

Q Now I'm going to actually ask you a different question. It is assume the same facts in this case except there's no bowel inflammation noted at all. There's no bowel symptoms. Is your opinion the same?

A What other symptoms are there?

Q It's the same clinical presentation as this case.

A Once again I can't answer that, and I'll explain why. The clinical presentation and the records on which I relied are so heavily influenced by the bowel inflammation that I really can't tell if something else was happening.

If I did not have the bowel inflammation there might have been something else. For example, there might have been immunodysfunction because of recurrent infections, for example, and a recurrent infection obviously is a chronic inflammation.

So for what I can say, this is it. You probably have looked at the medical records and seen how stormy this course was.

Q So the bowel inflammation is critical to your opinion?

A No. In the case of Michelle Cedillo, the bowel inflammation, it fixes it so that I don't have to move any further, so it's easy for me.

Q So any absence of any other bowel inflammation alone is enough?

A If there were no other bowel inflammation --

Q No other symptoms here other than bowel inflammation and MMR. I just heard you say that it's so striking to you in this case and important to you.

A Yes.

Q Would you need any of the other symptoms that you see? Is it the constellation of all these symptoms?

A It's mostly the bowel inflammation.

Q You also mentioned that there was recovery of persistent measles virus in your view.

A Yes.

Q Is that critical to your opinion here?

A It is critical that the measles virus caused an exaggeration inflammatory response, and it is

helpful in this case that she has been shown to have persistent measles virus.

If she did not have measles virus, persistent measles virus, and had no evidence that she ever had an abnormal response to measles then I think that we would have to rethink the case.

Q So do I take it then that the recovery of measles virus is not critical to your opinion?

A The recovery of measles virus is important in the case of Michelle Cedillo. However, if in fact she had had measles virus and was demonstrated to have had it, demonstrated in however you wanted to do it to say that it induced and started the inflammation, that would work as well.

Q I'm not sure I understand your answer. Is the recovery of persistent measles virus critical to your opinion or not?

A It is certainly critical in the case of Michelle Cedillo.

Q In the next case if you did not have that, the same facts, would you reach the same opinion?

A I think you would have to look at it. However, I'm trying to give you as cookie cutter as I can.

Q Maybe I could give you a different question.

A Okay.

Q If the next case came forward and there was not recovery of measles virus, can you tell us today that you would offer an opinion that it was caused by MMR vaccine?

A Right. Well, you know that there is going to be recovery of the measles virus at some point in time, right?

Q If it was recovered at I guess this would be seven years after the fact. If that was not there, would your opinion be the same?

A With Michelle Cedillo, yes. I'm sorry. Look, let me give you another scenario. Let me give you another hypothetical.

Q No. That's quite all right. I'm just trying to find out what the critical factors are, what your opinion is resting on. That's all I'm trying to find out.

I'm taking it that recovery of persistent measles virus is not critical to you. You would still reach the same opinion in another case even if that wasn't recovered.

A I cannot say that. However, I will say that if you want to come up with a box to put people in, one of the boxes that you can use is someone who has

persistent measles virus for the simple reason that that indicates an aberrant response to the measles virus.

Q So outside of this case, regardless of whether there's recovery of measles virus, you're not willing to render an opinion?

A I would certainly want to look at the case.

Q And you aren't reaching an ultimate conclusion about whether the MMR is causing autism?

A No, I'm not.

Q If you don't have the evidence of immune dysregulation, if there's an immune test and there's no evidence of immune dysregulation, is your opinion the same?

A Can I have a clinical evidence?

Q The same clinical picture as in this case, but there's no test done by Dr. Gupta.

A Okay. No lab tests. None by Dr. Gupta. There's no clinical evidence of any kind of immune --

Q No. The same facts other than there's no lab tests done by Dr. Gupta.

A I think we do not have to use those lab tests. We can use the exaggerated response to the measles virus in the form of the high fever and also in the form of the persistent measles virus in the

gut.

Q What if there were immune tests, but they were normal? Same fact situation.

A I would say the same thing. The laboratory tests help bolster my opinion in the case of Michelle Cedillo. However, in clinical medicine the clinical is always given precedence over laboratory tests. Laboratory tests are used to bolster that.

Q So in your view the results from Dr. Gupta would bolster your opinion, but if they were normal your opinion would be the same?

A Yes.

Q You talked a little bit about your qualifications, and I'm going to skip to those right now after we've gone through your theory.

A My opinion.

Q I'm sorry. Your opinion.

A Thank you.

Q You're not certified in allergy and immunology, are you?

A I'm board eligible. I have not taken the test. Instead, I did the three-year fellowship in clinical immunology and practiced allergy for 25 years.

Q Why didn't you take the test?

A Because at that time it was a very long time ago. At that time it only really qualified you to treat allergy, and at that time I thought the practice of allergy was extremely boring and I would never plan to do it, so then I went on to do it for the next 25 years.

Q So you practiced without being certified?

A I practice, yes. I'm boarded in internal medicine.

Q But you called yourself board eligible?

A Board eligible in allergy immunology, yes.

Q Is board eligible a phrase that's recognized by the organization that certifies allergists and immunologists?

A Yes, it is, so therefore if you are filling out an application, for example, like I'm a fellow in the American Academy of Allergy and Immunology. If you're filling out an application for that they will ask you whether you are boarded in allergy immunology or whether you're board eligible in allergy immunology.

Q You'll see on your screen a letter from the American Board of Allergy and Immunology referencing your status with that organization. They note that the board neither recognizes, uses nor defines the

term board eligible.

A Okay.

Q So you've been essentially representing that that is a qualification that you have in terms of rendering an opinion about immunology?

A Yes, I have.

Q You also mentioned, and you have this in your CV as well, you've been testifying about it, that you were on the team that developed Enbrel.

A Yes.

Q You mention in your resume that you're the medical director of the four doctor team responsible for filing the Biologics License Application for Enbrel?

A I'm sorry. Would you say that again?

Q You indicate in your resume that you were the medical director of the four doctor team responsible for filing the Biologics License Application for Enbrel?

A That is not exactly correct. I was a consultant medical director. There were I think either four or five physician members of the team.

It was run by a physician that the head of the team was a woman named Dr. Leslie Garrison, and she was the person who spearheaded the entire Enbrel

approval and was then made a vice president of Immunex as a result of that.

Q So that part is perhaps a misstatement on your curriculum vitae?

A My title was consulting medical director.

Q If we were to check the files at FDA to see whether your name appears at all on any of the documents submitted by Immunex for Enbrel, would your name appear?

A I'm sorry. I don't know. I don't know the requirements to submit members of the team.

Q So you don't know whether it appears or not?

A No, I'm sorry. I don't.

Q Was your role in it major or minor?

A I was one of five doctors. Would you like me to tell you what I did?

Q I'm trying to find out. You've represented that you were the medical director on the --

A No. I said consulting medical director.

Q I'm sorry. I meant on your CV. All right. You're the consulting medical director then on the BLA. That's the Biologics License Application.

We checked at FDA. Your name doesn't appear on any of the documents submitted by Immunex on the Biologics License Application.

A Okay. That's information. It doesn't make any difference because what I did is -- I told you what I did.

Q You talked this morning about Nottingham University.

A Yes.

Q On your CV you say that you're still a member of the faculty there. Is that true?

A No. I think I dropped off. The main purpose for me being at University of Nottingham is because my research was done there, and it was performed and supervised on a day-to-day basis by a physician named Dr. Mike Price.

Sadly, Dr. Price died of cancer in like about 2002, 2004, something like that, so when he died there was no longer a reason for me to be at Nottingham University.

Q So your CV is inaccurate? You are not still on the faculty of Nottingham University?

A That's correct. It sounds like it's an old CV.

Q Your CV also lists you as a faculty member at University of California-San Francisco. Are you still a member of that faculty?

A To my knowledge I am, unless this hearing

has kicked me off.

Q We checked with University of California-San Francisco. What was your faculty role at University of California?

A I'm on the adjunct series.

Q What did you do there?

A I did research in poison oak and ivy dermatitis, went on rounds with the docs.

Q How long ago was that?

A I'm sorry?

Q How long ago was that?

A Let me see. Through from about 1974 through about 1981, and then I went back again in 1984 and was there episodically probably through about two years ago.

The main reason I would use that is because when I would have different projects in different areas of medicine I would use that position then to go and do rounds or go in the clinic with the different docs.

For example, when I was asked to evaluate the children in the U.K. for immunodeficiency disorders I spent three, four months in the immunodeficiency clinic just to find out what was new.

The same thing for when I was doing atopic

dermatitis, connective therapeutics. I then started doing rounds in the atopic dermatitis clinic just to find out what was going on, what was new.

Q So you would do some rounds sporadically to aid your litigation consultation?

A Neither of those were litigation. Those were all biotech.

Q In the U.K., that was not litigation?

A Oh, in the U.K.? Sorry. In the U.K. it was litigation. The atopic dermatitis, psoriasis, et cetera, was for research for biotech companies.

Q How long ago was the research for biotech companies being done?

A I'm not absolutely sure. I think I did some multiple sclerosis clinics. I'm trying to remember the consultants.

Probably the atopic dermatitis was in about 1998, and subsequently I have not -- no. Then I went back to some of the immunodeficiency clinics, so I can't remember. You know, I go back and forth.

Q Okay. About a decade ago for the dermatitis? About a decade ago for the dermatitis?

A About, yes.

Q Any other involvement at UCSF, at University of California-San Francisco?

A Well, I use their library and I go to their parties, and also -- I'm sorry. I forgot. I took a regular -- let's see. It was a four month course in advanced biostatistics, clinical epidemiology and one other thing last year, so I was there like four days a week for probably the duration of the semester, which was about four months.

Q They in their response indicated that your participation was I believe at best gave very occasional lectures.

A Oh, no. That's not true. I don't know why they said that. Maybe they just don't know. Who did it come from? Oh, Bruce Wintroub?

See, Bruce Wintroub is the head of dermatology, right? This was in biostatistics.

Q You worked there in biostatistics?

A No. I took the courses in biostatistics.

Q You took courses?

A Yes.

Q Okay. So this is not as a faculty member. This is as a student?

A Well, I mean, I was allowed in because one of the requirements is -- one of the pops that you're in is that you need to be a faculty member and so that's the reason I was allowed in the class. It's a

special graduate class.

Q So this wasn't lecturing by you? This was not lecturing by you? This wasn't teaching by you, was it?

A No. I was on the receiving end of it. I was taking the classes and taking the tests.

Q Now, in the last decade, about the last decade, you've only seen patients in consultation for litigation purposes, correct?

A They're not specifically for litigation purposes, but they're to decide whether or not litigation is going to be warranted.

I'm asked to see them in my capacity as a medical toxicologist so, for example, I go out in the field and see a whole bunch of patients at a time doing histories and physicals and lab tests and then evaluate whether or not -- you don't want me to finish?

Q No.

A Whether or not they have any symptoms that are consistent with an environmental exposure.

Q You don't clinically treat these patients, correct?

A I usually will liaison with their treating docs. If I find something that concerns me I will

either call up the treating docs or send them letters because they're generally in different states.

Q Do you recall testifying in a case in February of this year, a vaccine case?

A Probably. Was that you?

Q Yes, it was.

A Hello.

Q Welcome back. Now, do you recall what your answer was about whether you treated patients or whether you saw them in consultation for litigation purposes at that time?

A I'm sorry. I don't.

Q Would it refresh your recollection then to know that you testified at that time that for approximately the last 10 years you had only seen patients for litigation consultation purposes?

Do you recall that? Do you recall testifying to that?

A No, I don't remember that, but I'm trying to remember if that's correct.

I don't think that's exactly correct because we sold our medical practice in -- I don't know -- 1996, 1997, something like that, and I continued to see patients in that same clinic, which is at 500 Sutter, for probably say through the year 2000, and

then I stopped. I would say that I would need to change that answer to something like seven years.

Q I don't think the decision has come out, so there's still time.

A I can't hear you. What?

Q I don't think the decision has come out yet, so there's still time.

A Are we going to win?

Q In your report you talk at length about immune suppression. Do I understand that your testimony really or what your opinion really hinges on is immune dysregulation? Is that right?

A You're absolutely correct, yes.

Q So it's not immune suppression that's important to you; it's immune dysregulation?

A It is immune dysregulation, and I'm sorry, but I don't find any at least major header in a quick look of my report where I talked about immune suppression, particularly in relationship to Michelle Cedillo. Would you like to point me to a page?

Q I'm just asking you. I took it from your testimony that from your report that immune dysregulation and not immune suppression is the critical factor for you.

A It is immune dysregulation because immune

dysregulation encompasses both immune suppression and an autoimmune disease.

And as you will remember I believe you and I agreed, or at least Dr. Kennedy testified, that the persistent measles virus is a manifestation of a type of immune suppression, which would fall under the umbrella of immune dysregulation.

Q So within that umbrella of immune dysregulation is it immune suppression that's important to you, or is it a skewing of the TH1/TH2 response that's important to you?

A It's all of it.

Q Neither makes a difference? It doesn't make a difference for your opinion?

If the person is immune suppressed and that's what the finding is, as opposed to immune skewing, your opinion stays the same?

A Both of them would be responsible for persistent measles virus, which is what she had.

Q Immune suppression would and the skewing?

A Either one, yes.

Q So we don't need to then talk about it. We have immune suppression. We don't need to talk about immune skewing, TH1/TH2 skewing? It's enough for you if there's immune suppression?

A I think so. Just a moment. I've just been handed my report, which appears to be the same document as I have in front of me.

Either TH1/TH2 skewing, that would suppress the ability of the body to clear the virus. Alternatively, immune suppression would affect the ability of the body to clear the virus. Both of them could result in prolonged measles virus present in the gut, which would then trigger off the chronic bowel disease.

Q What level of immune suppression do we need to see for you to opine that there is sufficient immune dysregulation for the measles virus to persist?

A I'm sorry. I can't answer that because the immune suppression and abnormal handling of virus has ranged from at least in animal studies, if I remember rightly, mild or moderate immune suppression through to the immune suppression that you see with HIV disease.

Q So sometimes immune suppression won't make a difference? You can have immune suppression, and you'll still clear the virus? Is that right?

A It depends on which arm of the immune system is suppressed, but that is certainly possible.

Q Let's be clear then. Immune suppression

overall, general immune suppression, both in the TH1 and the TH2 arm versus the skewing theory, which I'm not talking about right now.

I'm talking about your opinion that any immune suppression, just talking about lowering the body's level, the immune system's level to respond. My question to you was how far down does that have to be lowered for there to be persistence of measles virus?

A I don't know, and I believe no one knows.

Q If there is some lowering of the immune response, the immune suppression, do you expect there still to be clearance of the virus in cases?

A That's a question that I can't answer.

Q You're an immunologist. Do you expect that in some cases there will be clearing of the virus?

SPECIAL MASTER HASTINGS: Mr. Matanoski, can you keep your voice up as best you can?

MR. MATANOSKI: I'm sorry.

SPECIAL MASTER HASTINGS: I'm having a little trouble.

Did you understand the question?

THE WITNESS: I think so. He's asking whether or not if I only have TH1/TH2 skewing, but I have no other indication of other abnormalities of the

immune system, if it could result in persistent measles virus, and that answer is yes.

MR. MATANOSKI: No. That wasn't my question.

BY MR. MATANOSKI:

Q My question is immunosuppression distinct from TH1/TH2 skewing. This is a systemic immunosuppression?

A Yes.

Q Do you agree that in that instance there could be systemic immunosuppression and the body will still clear measles virus?

A It's possible.

Q Isn't there proof of it?

A Just a second. It's possible, particularly if the arm of the immune system that is suppressed is the antibody arm, but there is still an intact T cell arm so that you can still clear the measles infected cells.

Q And isn't there proof that you can clear measles virus cells in the presence of immune suppression?

A I'm sorry. As I sit here right now I don't know what you're talking about. Do you want to give me a paper?

Q I believe you may have discussed either in your report -- I think it was in your report -- about HIV patients.

A Yes.

Q They clear the virus, don't they?

A No, they don't.

Q They don't. They continue to persist? It persists lifelong in HIV patients?

A Well, I don't know if it's lifelong, but, you know, one of your own experts has published a paper saying that in HIV disease you have persistent virus.

Q And it clears. Isn't that right?

A I can't remember. I remember that she carried it out for like six months.

Q It's not important to you whether that would be true or not in the case of an immune suppressed individual?

A It's not important that we --

Q It's not important what the result of that study was?

A The result of the study was that there was persistent measles virus in the HIV infected children.

Q And if it were shown that it was cleared would that be important to your opinion?

A It depends on when it was cleared. It was my memory that it was cleared in about six months.

Q And that's not good enough?

A That would be good enough. Certainly. If in fact the persistent measles virus then produced a chronic bowel inflammation, then yes.

Q Okay. So if there's chronic bowel inflammation regardless of whether the persistent measles virus is clear?

A I don't know. You're twisting it all around. It's possible certainly.

Q Isn't your opinion that chronic bowel inflammation is caused by persistent measles virus?

A Yes. Triggered by it.

Q So it continues on its own?

A Yes.

Q So you don't need recovery of measles virus?

A Yes. That's the point I was making.

Q I see.

A You're going to get recovery of measles virus for at least --

Q And are you a gastroenterologist?

A Stop, stop, stop.

SPECIAL MASTER HASTINGS: Let her finish. Let her finish.

THE WITNESS: Thank you. For at least two weeks to four weeks after you have the vaccination in a normal person.

If that person then develops an autoimmune disease in an organ like the bowel where the virus is shown to be, then it obviously indicates that you've got viral persistence and that it strengthens your opinion that the trigger is the measles virus.

BY MR. MATANOSKI:

Q So you don't need the Ulhmann study. You don't need recovery of measles virus. You don't need anything but inflamed bowel?

A I need inflamed bowel in somebody who had an abnormal reaction to measles virus.

Q And the abnormal reaction is fever?

A It could have been the high fever, or it could have been the presence of a persistent virus.

Q So you're going farther than any of the other researches who have published papers?

A I certainly hope I'm not.

Q They've published papers, the researchers that we've been looking at and as have been cited by you, that indicate that it's persistent measles virus in the bowel that's causing the problem.

A It is persistent measles virus in the bowel

that triggered the problem. I do not know -- wait a minute. Stop.

I do not know if they said that the virus had to persist for four years. I can't remember if they said that.

Q These researchers are undergoing great lengths to try to recover measles virus from a bowel. Some of your experts came in here and -- I'm sorry. Not yours.

Some of the Petitioners' experts came in and talked about ongoing studies to do this, but in your view the recovery of measles virus is not necessary because it doesn't even matter if the measles virus is still there?

A It matters if there was an abnormal response to the measles virus particularly directed to the bowel, but in their case the abnormal reaction was the persistent measles virus in the gut.

I'm saying that there could be another scenario where you have an abnormal reaction to the measles virus that is manifest some other way, and you can't do a cookie cutter for this.

Q You've never worked with measles virus, have you?

A Just as a clinician.

Q So in other words you have treated some kids with measles virus?

A That's correct.

Q You never published on measles virus?

A The only publication I have is that one that Dr. Kennedy and Dr. Marchulonis and I did together with measles virus.

Q So other than that there's been no publication on measles virus?

A To my knowledge, from me that's correct. There's obviously a lot of publications on measles virus.

Q And that's your only publication on measles vaccine or MMR vaccine?

A Yes.

Q And you and Dr. Kennedy and Dr. Marchulonis worked together on that publication?

A Yes.

Q And all three of you were consultants in the U.K. MMR litigation, correct?

A Yes.

Q And that's how you met each other?

A Oh, no.

Q You knew Dr. Kennedy beforehand?

A I knew Dr. Marchulonis since about, let's

see, 1976, and I had known of Dr. Kennedy. However, Dr. Marchulonis was the one that asked Dr. Kennedy to be involved when we found we needed a viral immunologist.

Q Did Dr. Marchulonis bring you into the U.K. MMR litigation?

A No. Actually, it was Ms. Sylvia Chin-Caplan that did.

Q She brought you into the U.K. MMR litigation?

A She suggested to the attorneys in the MMR litigation, who said that they needed a clinical immunologist to evaluate the relief criteria, that they might call me.

Q Do you recall how much money you received for your participation in the litigation there?

A I'm sorry. I don't. I will tell you that I spent a lot of time on it.

Q This is represented in pounds sterling. Does 115,107 pounds sterling sound about right?

A I'm sorry. I can't tell you that. I can tell you that I worked on it from about 1999 through like around 2003, and I spent a lot of time on it.

Q We've been talking a lot about the vaccine. Do you know how the attenuated measles vaccine is

made?

A I have known, and I don't remember right now, but I do know that the relief criteria is simply that the measles vaccine should produce a plaque that is equal to or less than the side of the plaque that is produced by an equivalent number of wild-type viruses.

I also have looked at genetic mapping of the different measles vaccine strains, and to my eye it seems that they have not actually been able to identify the part of the DNA which is mutated which is responsible for its attenuation, and that's about the limit of it.

Q Do you know how they make it?

A Yes. They made it a long time ago by passing it multiple times through whatever cells they grew it in.

Q Do you know what kind of cells they grew it in?

A Let me see. I seem to remember that they were chicken cells. At least they were chicken cells when they were making the thing.

Q When you introduce attenuated measles vaccine in the body, do you know what the properties are?

A Yes.

Q What it does? What does it do?

A Roughly from a clinical standpoint it induces immunity, which is not as long lived as the wild-type measles, and the only immunity that they measure are antibodies. I have not really seen any studies on large vaccinated populations where they're looking at the T cells.

It produces disease which is less in nature than that of the wild-type. In other words, the symptoms are attenuated.

Q Does it replicate as readily as the wild virus?

A I do not think it does.

Q So part of the attenuation process has limited its ability to replicate. Is that right?

A That's my understanding. I would prefer to defer to Dr. Kennedy because that's the reason we brought him in as an expert for you.

Q Because he has some familiarity with measles virus?

A What?

Q Because he had familiarity with measles vaccine virus?

A Because he has familiarity with vaccines in

general. Yes.

Q With the immune suppression you were talking about after wild measles virus or with the vaccine virus does the level of immune suppression depend to any extent on how severe the infection is?

A I do not know that.

Q You mentioned in your report that you've published extensively on environmental toxins.

A I did? I have certainly worked extensively on environmental toxins. My publications have been limited to a couple of papers involving the affect of trichlorethylene on the immune system, and then also I worked on HIV, which you could certainly consider an environmental agent. HIV, tricosanthin, those papers which were clinical trials.

Q In your report you indicated that the environmental toxins that you published on were poison oak and poison ivy.

A I did, didn't I? I told you I was one of the world's experts.

Q Now, are you sure you published on TCE?

A Yes.

Q Have you ever published on hexavalent chromium?

A I have never published on it. I have done

litigation research on it.

Q You did testify about it, correct?

A I can't remember if I actually testified in that case or not.

Q You at least offered litigation support then or consultation on hexavalent chromium?

A Yes, I did.

Q You never published on dioxin, did you?

A I have not published on dioxin. I'm in the process. There's a manuscript in preparation on dioxin.

Q You testified in a case involving dioxin, didn't you?

A I can't hear you.

Q I'm sorry. You testified in a case involving dioxin, didn't you?

A I don't think that ever went to Court. I believe that was one of the ones that was settled.

Q That was another instance where you were a litigation consultant?

A Yes. Well, I was a testifying expert, but they never went to trial.

Q Now, you mentioned a moment ago you think you might be having a publication coming out soon on dioxin?

A Well, I'm in the process of writing the report.

Q It hasn't been submitted to any journals?

A That's correct.

Q Any other co-authors on it?

A Well, yes. My colleague, Bob Baldwin.

Q I've been through your CV a little bit this morning. Any publications that you have that aren't on that CV?

A I don't think so. I think the most recent one is the one that Kennedy, Marchulonis and I did, and if in fact that's on the CV then you probably have an up to date one as far as publications go.

Q So that's the extent of your publications?

A I felt it was enough.

Q Now, you've described yourself as a medical toxicologist?

A Yes.

Q What training have you had in toxicology that's not reflected on your CV?

A The formal training has been when I was a medical student. Subsequent to that, though, I have done medical toxicology in two different aspects. The first is of course I've worked for my whole professional life for pharmaceutical companies and

biotech companies, and nowadays a medical consultant to the medical director actually works in large part as a toxicologist because of course the efficacy is the remit of the statisticians.

So, you know, you spend the day trying to decide whether or not the adverse events that you're witnessing are part of the normal disease process or other drugs are associated with your drugs. Then the other aspect of that is that I started looking at environmental toxicology in 1984. Well, no. I had done that before.

I actually started in the field in about 1976 when I submitted a grant supported by a small study looking at the immune system of the farm workers in the Central Valley because they were being exposed to pesticides, and essentially I've been doing environmental toxicology off and on ever since then.

Q And you said your training primarily came as a medical student?

A The formal training came as a medical student, but the on the job training has continued from about 1984.

Q The name of your consulting company is Immunology Incorporated? Is that right?

A Yes.

Q You offered a great deal of testimony this morning on mercury. Have you ever published on mercury?

A I have not published on mercury.

Q Turning to your slides you start off with the first slide Immunotoxicology of Mercury in Humans. What kind of mercury are you referring to when you talk about that? What are the species of mercury?

A I'm sorry?

Q What are the species of mercury?

A The species of mercury that I am referring to I'm getting primarily from Dr. Aposhian because I have no particular expertise in the differences, for example, pharmacokinetics, et cetera, in the species of mercury. I'm told by Dr. Aposhian that there are differences, so I have to be careful. The mercury species that I'm aware of are ethyl mercury, methyl mercury, inorganic mercury, iron and then mercuric vapors.

Q So you said that you don't have any particular expertise in the pharmacokinetics of the various species of mercury?

A I do not. I turned to Dr. Aposhian for that.

Q Okay. So you're relying on him for the

pharmacokinetics of mercury?

A Yes, I am.

Q Would immune suppression be a pharmacokinetic of mercury?

A No.

Q It is not a pharmacokinetic property?

A No.

Q You mentioned that you were I believe you put it papered out of your office when you were downloading I take it articles on mercury?

A No, not when I was downloading them, when I was printing them.

Q Sorry. When you printing them. That makes sense. Yes. Do you know what the species of mercury were in those articles that you were reading?

A In most cases the species were described, and it was the whole range.

Q It was all the different species?

A It was.

Q You would agree from your training in toxicology that there's a difference in how the different species of mercury affect the body, correct?

A Yes, and not just on my training, but also, I have been educated by Dr. Aposhian.

Q Educated by Dr. Aposhian?

A Aposhian. Yes.
Q For this trial?
A Well, not specifically for this trial, but for the investigation of mercury in the human body.
Q For litigation purposes?
A For litigation purposes. Yes. We've had several meetings.
Q So there's more than this trial that you're preparing your opinion for and studying under Dr. Aposhian for?
A Yes.
Q How much of thimerosal is ethyl mercury?
A Let me see. I'm told that there is about 50 percent of mercury in thimerosal, and I know that thimerosal is composed both of ethyl mercury coupled to salicylic acid, so I can't tell you how much is ethyl and how much is the salicylic acid. I think I actually said that in the testimony this morning because I got that from either the Goth or the Agrawal paper.
Q What's the periodic chart symbol for mercury?
A Hg.
Q What's the molecular weight?
A I can't remember.

Q Can't remember? Do you know?
A I'm sorry?
Q Do you know?
A I would look it up.
Q What's the chemical composition of thimerosal expressed as elements on the periodic chart?
A You know, I don't really understand that question.
Q You told me what the element was, mercury, what it was described as on the periodic chart, Hg.
A Yes.
Q What are the other elements on the periodic chart that describe thimerosal that compose it?
A Hydrogen, oxygen, sulfur, carbon.
Q Do you know how they're aligned?
A I can't hear you.
Q Do you know how they are aligned?
A What do you mean aligned?
Q Bonding?
A The bonding.
Q What's double bonded? What's single bonded?
A I mean, I think I do, but I'm not positive, and so I don't want to speculate.
Q What's the chemical composition of ethyl

mercury expressed the same way?

A Let me see. Ethyl mercury is C2H4 I think.

Q Do you know how they are bonded?

A No, I don't.

Q From a toxicological significance standpoint what's the clinical significance of the difference of methylated mercury and ethylated mercury?

A I'm told that there's many differences.

Q Who told you this?

A Dr. Aposhian.

Q Okay. So this again was in preparation for this litigation?

A Not necessarily this litigation.

Q For litigation on mercury?

A Thimerosal. Yes.

Q So what is the difference?

A There is a difference in the half life, there's a difference in the association forming the inorganic mercury or the Hapten whatever. I mean, what I would do is if you actually ask me to answer these questions I would go to him or I would look up in an article and I would make lists.

Q You've just offered I don't know maybe a half hour of opinion on the toxicological affects of mercury. You've offered 14 pages of slides on the

toxicological affect of mercury. So you're telling me that you need to actually ask someone else and answer about the differences between methylated and ethylated mercury, how they affect the body?

A I would ask for somebody else's opinion on how they affect other organs apart from the immune system. My responsibility was to look at the immunotoxicity of mercury, and that's the reason that I gave you the entire broad range. Most of the 14 slides I was careful to tell you involved either methyl mercury, ethyl mercury, mercury vapor, inorganic mercury, whatever.

Q Let's go to the first slide. Mercury and the immunotoxicology of mercury is the --

SPECIAL MASTER HASTINGS: Which slide are we turning?

MR. MATANOSKI: This is Slide 12.

SPECIAL MASTER HASTINGS: No. 12. Okay.

BY MR. MATANOSKI:

Q You mentioned in that it inhibits oxidative burst and neutrophils causing neutrophil dysfunction. Of the species of mercury, which one were you relying on?

A I can't remember what the paper was. You would have to put the paper in front of me.

Q You didn't cite any reference. What is your best reference for that?

A I'm sorry. As I sit here right now I do not know the references, and I'm sorry that they weren't on the slide. However, I'm told that I can have an opportunity to do rebuttal testimony or something. If you specifically ask for all of those references you will get them.

Q Doctor, you were supposed to put together an expert report in this case by February 20, 2007, that laid out in detail your theory of the case.

A Who told you that?

Q So you didn't think that you had to lay out in detail your theory of the case when you filed an expert report in this case?

A I was told that I should file an expert report. I do not remember the date at which I did so, and it's my opinion that I laid out an expert report. I gave you the limitations of the statement on the slide, and I have also told you that there is a report that I have put together which gives you all of the references including all of the references that they refer to. I simply did not include it in this report because I didn't think it was important. It exists, and you may have it.

Q That's not rebuttal, doctor, that's supposed to be your opinion. That was supposed to be laid out four months ago so that our case could be presented in response to your opinion.

A I have no information as to your legal schedule.

SPECIAL MASTER HASTINGS: Do you have a question?

MR. MATANOSKI: I do, sir.

BY MR. MATANOSKI:

Q You filed a seven page, single spaced report. In that report you have one paragraph that discusses the affect of mercury on the body, and in that you cite two articles, Goth and Agrawal. What other support do you have for your opinion here today? You've given us 14 pages of slides discussing mercury.

A The reason you have those 14 pages is because I had thought that Dr. Aposhian was going to opine on the immunotoxicity of mercury, and I was listening to his testimony on Monday and found that he was not going to do that, so therefore I felt it was important for me to add stuff so that the Court could have access to it.

Q Okay. So you're adding stuff about toxicology?

A About immunotoxicology of mercury. Yes.

Q Why did you think Dr. Aposhian was going to talk about immunotoxicology?

A Because I was told that he was going to be discussing toxicology of mercury in general, and to me that included immunotoxicology.

Q So you thought he was qualified to talk about immunotoxicology?

A I'm sorry, I didn't know. I've not seen his CV, and of course we weren't allowed to talk before the trial.

Q You weren't allowed to talk before the trial?

A I'm sorry?

Q I thought you did talk with him. He talked to you about mercury.

A Yes. I talked to him maybe months ago. We've had several meetings where he has presented the toxicology of mercury, so I was surprised when he did not include the immunotoxicology, and I decided that it was necessary for me to give the Special Masters a complete overview of it.

Q So Dr. Aposhian's testimony was incomplete?

A I can't hear you.

Q So Dr. Aposhian's testimony was incomplete?

A Dr. Aposhian did not include the immunotoxicity of mercury.

Q Who informed you you weren't supposed to talk to the other testifying experts?

A I was told by the attorneys.

Q The attorneys told you you shouldn't talk to one another?

MS. CHIN-CAPLAN: Special Master, we're getting to the area of attorney/client communications here.

SPECIAL MASTER HASTINGS: Is there any relevance to the question, Mr. Matanoski?

MR. MATANOSKI: I'll move on.

SPECIAL MASTER HASTINGS: Go ahead.

MS. CHIN-CAPLAN: Can Petitioners take a five minute break?

MR. MATANOSKI: I'm sorry, sir. I can probably finish up before our lunch break.

SPECIAL MASTER HASTINGS: All right. Let's take a five minute break, and then we'll finish up.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We'll go back on the record here. We'll be continuing with cross-examination.

MR. MATANOSKI: Thank you, Your Honor.

BY MR. MATANOSKI:

Q Doctor, do you have cites for each of the statements that you have in your slides regarding toxicology?

A Regarding the toxicology of mercury? Is that what you want to say?

Q Yes.

A Yes, I do have that.

Q Can you provide those in the next 24 hours?

A I'm sorry. I can't do it in the next 24 hours because my travel schedule will not allow it. However, I will do it in a very timely fashion.

Q Can we go through them now, and we'll find out the ones that you can remember right now? Your best ones that you can remember?

A No. The two that are most relevant for the specific mercury that I feel is applicable to this case, I have given you those references.

MS. CHIN-CAPLAN: Special Master, if there's any question about the literature that Dr. Byers has provided us we will get it, and we will file it as soon as possible. We'll talk to her today about this.

SPECIAL MASTER HASTINGS: I understand.

MR. MATANOSKI: It just makes it very difficult to cross-examine a witness if you don't know

what they're relying on.

SPECIAL MASTER HASTINGS: Well, I mean, you --

MR. MATANOSKI: I understand.

BY MR. MATANOSKI:

Q Doctor, do the normal immune parameters vary with age?

A Yes, they do.

Q Is it standard practice to use adult values to assess a child's immune system?

A It is standard practice.

Q You mentioned the PCR testing that was done in this case?

A I did not.

Q I thought you mentioned the recovery of measles virus genomic material through PCR or the detection?

A I was told by one of the PCR experts that in fact the measles virus had been recovered, and that's what I'm relying upon. I know that there is several different types of PCR, and so I don't know and I can't answer the specific test.

Q The PCR test, though, you would accept in this case, the diagnostic values from that test? Are they important to your opinion?

A It's important for my opinion to know that measles virus was retained in the gut.

Q Okay. And that was detected by PCR?

A And that was detected by a test that the experts upon whom I'm relying feel is sufficient.

Q Your own opinion on PCR? Do you have an opinion on the value of PCR?

A I do not.

Q Did you offer an opinion previously to this Court on the value of PCR?

A No. I offered an opinion on my reliance of the other experts.

Q I'm sorry. Previously in testimony before this Court in another case?

A I'm sorry. I can't remember.

Q Do you recall testifying that PCR was not reliable unless it was an FDA-approved lab?

A I'm sorry. I can't remember doing that at all.

Q You don't hold that opinion now?

A I haven't thought about it.

Q Would it be important to you that it be an FDA-approved lab?

A Well, first of all you know that labs are not directly accredited by the FDA.

Q I was going over your testimony, doctor.

A I'm sorry?

Q I was going on what was important to you based on your testimony.

A The laboratories are accredited by the American College of Pathology. Certainly, if it was a routine test you would prefer to have it done by an accredited laboratory. In some cases that's not possible. The reason is that if it's ACP accredited you don't have to worry about looking at the controls. You don't have to do that yourself because somebody else has already done it for you, namely the American College of Pathologists.

If, though, you're looking at a test that's done by a different laboratory that is not certified by the ACP then either you have to do it yourself or you have to find somebody else upon whom to rely, and that's what we've done here.

Q I'm sorry. I'm not sure I understand whom you're relying. As far as testing for controls?

A Talk a little louder, please.

Q I'm sorry. For testing for controls?

A Not just testing for controls. You're making faces at me. You are.

SPECIAL MASTER HASTINGS: Look at the

Special Masters. You won't make the case today.

THE WITNESS: She's much more attractive. Thank you. If you have a test or a lab that is accredited by the ACP, American College of Pathologists, then they have already looked to make sure everything is kosher. They have made sure that the controls are kosher, and probably as important like about five times a year they send out unknown samples to make sure that you get the right results, so somebody has already done all that work for you.

If you however are using a laboratory, for example, an academic research laboratory or even a clinical laboratory where that has not been done then you either have to go in yourself and convince yourself that all of their controls and their normal ranges are proper or alternatively you have to ask an expert upon whom you can rely to do it. So it just makes it a little more complicated.

BY MR. MATANOSKI:

Q And you don't recall testifying that you would not credit PCR results from a non-FDA-approved lab?

A I'm sorry. I cannot remember doing that.

MR. MATANOSKI: Thank you. I have no further questions.

SPECIAL MASTER HASTINGS: Do you have some questions for this witness?

SPECIAL MASTER VOWELL: I have some questions, but do we want to take a lunch break first or do we want to just continue on? I mean, I'm just asking.

SPECIAL MASTER HASTINGS: Well, let me ask you, Ms. Chin-Caplan. Are you expecting to do a lot of redirect?

MS. CHIN-CAPLAN: No, Special Master, I'm not.

SPECIAL MASTER HASTINGS: Well, maybe we could go on and see if we conclude without a lunch break. We'll see what happens.

Go ahead, Special Master Vowell.

SPECIAL MASTER VOWELL: Bear with me, Dr. Byers, because I may have to flip back and forth a bit, and if my questions are not properly phrased, help me out. I'm trying to understand what you had testified about. As I understand it dendritic cells secrete cytokines.

THE WITNESS: Yes, they do.

SPECIAL MASTER VOWELL: And those cytokines can either be proinflammatory or antiinflammatory?

THE WITNESS: I didn't say that, but you're

correct. They can be.

SPECIAL MASTER VOWELL: Okay. Would you give me some examples that would be found in the literature of proinflammatory cytokines?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay.

THE WITNESS: The ones that most come to mind are TNF-alpha, IL6 and IL1-beta.

SPECIAL MASTER VOWELL: Okay. So TNF, and that's alpha.

THE WITNESS: TNF-alpha.

SPECIAL MASTER VOWELL: Okay. Tumor necrosis factor alpha.

THE WITNESS: That's right. That's the one that Enbrel and Remicade are directed against. IL6, which is the one that the new monoclonal antibody I was telling you about is directed against, and IL1-beta, which is new. You're probably not going to be seeing a lot of references to that unless you look at maybe the literature this year, and the reason for that is we just elucidated a new path which results in the secretion of IL1-beta instead of TNF-alpha.

So from your question it's obvious that you are becoming very well-read in the subject. So if you want to find IL1-beta look, for example, for the CIAS1

gene mutations because that's the literature where it's going to come from.

SPECIAL MASTER VOWELL: And IL1 is then divided into alpha and IL1-beta? Are there two sets? Were they originally thought to be part of the same?

THE WITNESS: (Nonverbal response.)

SPECIAL MASTER VOWELL: Okay. You're shaking your head, so obviously I've got something wrong. So go ahead.

THE WITNESS: IL just stands for interleukin, and so therefore all of the classes of interleukin are going to have IL as the beginning. Yes.

SPECIAL MASTER VOWELL: Right, but I'm talking about IL1-beta. Are they part of the same family of interleukins? I don't know how interleukins came to be numbered, so I'm assuming that originally we had something that was called IL1 and now its IL1-alpha and IL1-beta. If that assumption is incorrect please correct me.

THE WITNESS: I think you're right, but let me also just correct you on one thing. The cytokines by and large have been numbered in the order in which they were discovered, but sometimes they were numbered in different ways.

SPECIAL MASTER VOWELL: And I understand that people may have found the same one and called it something else, and then eventually the scientific community came to a consensus on what it ought to be called.

THE WITNESS: Sometimes they do, and sometimes they don't. I mean, what happens is that the gene jockeys sit around and they find something abnormal, and then they say well, let's call this fox pro three or let's call this toll-like receptors. Then at a later date the biologists come in and they say that's what that's doing.

Sometimes at a later date you have a big convention and you say, all right, we're going to change the name, and sometimes you never do.

SPECIAL MASTER VOWELL: Okay. And antiinflammatory cytokines, can you give me some examples of those?

THE WITNESS: No. As I sit here right now I can't because I just haven't thought about it, but I certainly will be willing to send you all the reprints that you want.

SPECIAL MASTER VOWELL: I think there are enough articles here for us to read, Dr. Byers.

THE WITNESS: Oh, dear.

SPECIAL MASTER VOWELL: Identifying which ones may be more helpful than any new ones. All right. You talked about helper inducer cells on one of your slides. Can you explain to me what they are?

THE WITNESS: Well, yes. The helper cells are *T* cells. The name is very old-fashioned, but basically they're called helper inducers because they will induce *B* cells to produce antibodies.

SPECIAL MASTER VOWELL: Okay. So the helper inducer cells are another name for *T* cells, and the *T* cells induce the *B* cells to produce antibodies and then you get an antibody response.

THE WITNESS: That's right.

SPECIAL MASTER VOWELL: That would be -- I'm losing my words here -- not the innate immune system, but the adaptive immune system?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay. As I understand your testimony about the affect of mercury in general, and we won't try to speciate it right now, that mercury in general has a toxic affect on the immune system.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: And you testified that it lowers suppressor cell numbers on Slide 12,

but you don't have a citation for that. You just don't recall that citation at all?

THE WITNESS: No, I don't. I'm sorry. I have prepared an entire brief with all the citations.

SPECIAL MASTER VOWELL: You referred us to the Agrawal and the Goth studies.

THE WITNESS: I did.

SPECIAL MASTER VOWELL: Maybe I misunderstood your testimony, doctor. You testified I think that the presence of mercury induces apoptosis in *T* cells.

THE WITNESS: It can. Yes.

SPECIAL MASTER VOWELL: Okay. How about dendritic cells?

THE WITNESS: No. I've never seen evidence that mercury induces apoptosis of dendritic cells. As I sit here right now I cannot remember it.

SPECIAL MASTER VOWELL: As I understood your testimony about Michelle you indicated that one of the things you would look for in clinically evaluating immune dysregulation -- I'm referring to page 2 of your slide -- would be a history of frequent and/or unusual infection.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: But you said that

was not present in Michelle.

THE WITNESS: You're correct.

SPECIAL MASTER VOWELL: And so there is no evidence from the number of infections prior to MMR vaccine that the thimerosal containing vaccines had any clinical impact on her presentation.

THE WITNESS: You're correct. She did have a varicella vaccination at age 12 months, and when we talked to her mom she could have had an abnormal reaction to it, but I don't have any records of it and so therefore I'm not saying anything about it.

SPECIAL MASTER VOWELL: Okay. You talk in general about the effects, and I'm referring to your Slide 31 here, of cytokines on the central nervous system, specifically interleukin-2 blackbox form.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Did you testify in any way about the affects of thimerosal containing vaccines on interleukin-2 levels?

THE WITNESS: I did not testify.

SPECIAL MASTER VOWELL: Or thimerosal in general?

THE WITNESS: Yes. One can postulate what might be the affect, but I do not know of any experimental data as I sit here right now.

SPECIAL MASTER VOWELL: Okay. So when you're talking about what interleukin-2 can do, change the hemostatus, speech difficulties, ataxia, you didn't cite me to anything that said there's a problem with interleukin-2 based on mercury exposure.

THE WITNESS: Indirectly, because the mercury exposure impairs the ability of the immune system to clear the measles virus. The measles virus then stimulates the adaptive and the innate immune systems. The adaptive immune system of course is one of the primary pushers of IL2, and so therefore one indirectly is asking the thimerosal to exaggerate the affect of IL2.

SPECIAL MASTER VOWELL: But you are not aware of any research that shows an affect on IL2 by thimerosal, or ethyl mercury, or methyl mercury?

THE WITNESS: I have not seen any papers where they have taken thimerosal and put them in *T* cells in a test tube and demonstrated that it decreased it.

SPECIAL MASTER VOWELL: How about interferon-alpha? That's Slide 32.

THE WITNESS: My answer is the same.

SPECIAL MASTER VOWELL: Okay. I'm just trying to track down that I haven't missed anything in

terms of the reading because I have spent a lot of time with Agrawal and Goth. And you indicated interferon-beta has the affect of depression, suicide, seizures, at least they've been reported, but you don't have any citations for an affect of the measles virus, or thimerosal, or any mercury affect on the production of interferon-beta.

THE WITNESS: I do not.

SPECIAL MASTER VOWELL: Okay. I'm just tracking this down. All right. You referred in one of your slides I believe to LPS. What is LPS?

THE WITNESS: Lipopolysaccharide.

SPECIAL MASTER VOWELL: And that is? Translate that for me.

THE WITNESS: Lipopolysaccharide is the component of several cell walls of bacteria. You'll remember I said that there's essentially 10 major specificities of the toll-like receptors. One of those is LPS, and I think LPS is probably the most potent of the stimulants of that pathway, and so therefore, it's a favorite of people who would like to simply use something to stimulate that pathway.

SPECIAL MASTER VOWELL: For the record that was on page 25 of Petitioner's Trial Exhibit No. 9. If I understand your testimony, Dr. Byers, you said

that because of the thimerosal containing vaccine in Michelle that contributed to her inability to clear the measles virus from her system. Was that your testimony?

THE WITNESS: Yes, I did.

SPECIAL MASTER VOWELL: Okay. And the presence of the persistent measles virus and/or the presence of the residual thimerosal in whatever form it's left in the body has an affect on cytokine direction?

THE WITNESS: Yes, it does.

SPECIAL MASTER VOWELL: And it is the proinflammatory cytokines that you think responsible for the gut symptoms and the CNS symptoms?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: And intestinal symptoms and CNS symptoms are linked?

THE WITNESS: Are?

SPECIAL MASTER VOWELL: Are linked? In other words, those people who have intestinal symptoms are more likely to have CNS symptoms. Is that what you're saying?

THE WITNESS: Than those people that do not have gut symptoms, and actually, probably than those people who have inflammation in other areas of the

body.

SPECIAL MASTER VOWELL: You also referred us to the Ashwood article. Is that correct?

THE WITNESS: I did.

SPECIAL MASTER VOWELL: And you talked about the significance of Michelle's CD4 levels. The CD4, CD8. In other words, she had a normal CD4, but the CD4, CD8 ratio was skewed?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Doesn't Ashwood talk about decreased CD4 levels in autistic individuals?

THE WITNESS: I can't remember.

SPECIAL MASTER VOWELL: So you couldn't tell me why Michelle's would be normal but Ashwood would find a decreased level?

THE WITNESS: I'm sorry. I can't.

SPECIAL MASTER VOWELL: That's okay. I'm just trying to answer questions that occurred in the course of the testimony and in the course of my reading of the articles. Do you recall from your reading of the mercury articles, Agrawal and Goth whether IL6 is increased or decreased as the result of thimerosal or some form of mercury?

THE WITNESS: In the Goth article, as I remember it was biphasic.

SPECIAL MASTER VOWELL: And what would the significance if any of it being biphasic be?

THE WITNESS: I think there's not very much significance because the biphasic nature of this is really not known. In other words, I mean, if you ask me, for example, there's a circadian rhythm of the immune system in general which we now know is responsible for the classic old-timey afternoon fevers in TB, but we knew about the afternoon fevers and then 40 years later we figured out about the significance of the circadian rhythm.

My guess is that this biphasic business is going to be under investigation for say the next 10.

SPECIAL MASTER VOWELL: Are IL6 and IFN-beta --

THE WITNESS: Are they linked?

SPECIAL MASTER VOWELL: How are they linked?

THE WITNESS: IL6 and IL1-beta?

SPECIAL MASTER VOWELL: IFN-beta.

THE WITNESS: Interferon-beta.

SPECIAL MASTER VOWELL: Yes. Are they linked at all?

THE WITNESS: They're linked in that they are -- let me see. I'm sorry. I can't remember how they're linked. I can give you TNF-alpha and IL1-

beta.

SPECIAL MASTER VOWELL: Okay. I think those are my questions. Thank you very much, doctor.

THE WITNESS: Thank you.

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, did you want to do some redirect?

MS. CHIN-CAPLAN: Yes, Special Master.

REDIRECT EXAMINATION

BY MS. CHIN-CAPLAN:

Q Dr. Byers, you submitted a report in this case, didn't you?

A I did.

Q And, Dr. Byers, on page 4 of your report, which is Petitioner's Exhibit 57, at the very bottom have you included a section on thimerosal and how it relates to the problems that Michelle Cedillo suffers?

A Yes, I did.

Q Okay. And, doctor, just read along with me.

SPECIAL MASTER HASTINGS: Which page did you say?

MS. CHIN-CAPLAN: Page 4.

SPECIAL MASTER HASTINGS: Page 4. Thank you.

MS. CHIN-CAPLAN: Thank you.

BY MS. CHIN-CAPLAN:

Q The other known immunosuppressive factor to which Michelle Cedillo was exposed was thimerosal in the vaccine she received before and shortly after the MMR injection. Mercury has been shown to be immunosuppressive in multiple systems both in animals' in vivo systems and human in vitro systems. One of the most consistent findings is a demonstration of abnormal increase in the TH2 population of helper *T* cells resulting in a skewing of the TH1 TH2 ratio.

Recent data indicates the root cause of this abnormal immune function is the dendritic cells. These cells of all the immune cells appear to be the most sensitive to the affect of mercury, specifically thimerosal. In murine dendritic cells thimerosal was shown to interfere with calcium channels thereby adversely affecting its cytokine production necessary for proper antigen presentation.

This occurred at relatively small amounts such as 50 nanomoles, about 11 micrograms per liter. Goth, et al., 2006. A more recent paper used human dendritic cells to establish that thimerosal treatment altered the ability of the cells to produce a TH1 response instead promoting a TH2 response. Agrawal, et al., 2007.

Again, at a dose of 50 nanomoles. Since

measles virus itself also produces the skewed response the thimerosal containing vaccines received both before and shortly after the MMR vaccination together with the immunosuppressive ability of the measles virus itself may have resulted in a prolongation of the measles virus in the body, and this should be included in the differential diagnosis of the abnormal immune system. Have I read that correctly?

A Yes, you have.

Q Has your opinion changed at all since you wrote that report?

A No. No.

Q So the testimony that you gave today is entirely consistent with what's contained in your report?

A I think so. I would have to go back and double check the doses because this is 50 and it might have been 25 nanomoles. But, yes, it's nanomole or amount. It's small.

Q So your testimony today is the same as what you let the government know back in February that you were going to be testifying about?

A Yes.

Q Doctor, there were some questions about page 12 of your slide, and it was titled Immunotoxicology

of Mercury in Humans. Mr. Matanoski was asking you some questions about why you didn't include any citations. Do you recall that?

A Yes, I do.

Q Now, doctor, you don't have an office here in Washington, D.C., do you?

A No, I don't.

Q You're functioning out of a hotel room. Isn't that true?

A Yes.

Q And you don't have any staff to help you, do you?

A No.

Q Other than me. Doctor, I'm going to show you page 12 on your computer screen. Do you have some articles cited to the right of this page on your computer?

A What's the right of the page mean? Excuse me. The right of this?

Q Yes. The page.

A Yes, I do.

Q Doctor, could you just tell the Court what those citations are?

A Yes. One is al-Hashimi, *Inhibition of Luminol Dependent Chemiluminescence of Human Granula*

Sites by Low Doses of Inorganic Mercury.

SPECIAL MASTER HASTINGS: Is there a whole lot of these? Okay. There's four? Okay. Go ahead.

THE WITNESS: Okay. So al-Hashimi.

SPECIAL MASTER HASTINGS: You're trying to make the point, Ms. Chin-Caplan, that there are citations here.

MS. CHIN-CAPLAN: Yes.

SPECIAL MASTER HASTINGS: And maybe we could make a copy of these and let the government have them rather than reading the whole thing into the record here?

MS. CHIN-CAPLAN: That's fine.

SPECIAL MASTER HASTINGS: Okay.

BY MS. CHIN-CAPLAN:

Q So, Dr. Byers, you relied on the medical literature that you printed up when you formulated these slides, didn't you?

A Yes, I did.

Q And there are citations available for this information contained on this page?

A Yes. I'm glad you said. But I also have a regular report that is available that will support the slides.

MS. CHIN-CAPLAN: Thank you. I have no

further questions.

SPECIAL MASTER HASTINGS: Any re-cross?

MR. MATANOSKI: Briefly, Judge.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

RECROSS-EXAMINATION

BY MR. MATANOSKI:

Q You said you have a regular report. Is that the report you submitted in this case? The regular report that supports these slides?

A There is a regular report, and I did not include it in that presentation, but I have it.

Q You don't plan to be filing that now in this case, do you?

A It depends on whether you want to. I thought you had just asked for it. In fact, you asked for it within the next 24 hours.

Q No. I asked for the cites, ma'am, and I understand we'll be getting those. You stated that was inorganic mercury as to the cite on the first part of Immunotoxicology of Mercury in Humans? Is that right?

A I'm sorry. I don't know what you're talking about.

SPECIAL MASTER HASTINGS: I'm not sure what the question is.

BY MR. MATANOSKI:

Q I'm sorry. On page 12 you were asked to read one of the citations. I take it it was for the inhibits oxidative burst in neutrophils causing neutrophil dysfunction. Did I understand that to be al-Hashimi? Is that right?

A I remember that, yes. I just read it.

Q On inorganic mercury?

A I can't remember.

Q I thought I heard Ms. Chin-Caplan read that out of the title.

SPECIAL MASTER HASTINGS: I thought they're going to print it out and give it to you within a few minutes.

MR. MATANOSKI: Okay. Thank you, sir.

BY MR. MATANOSKI:

Q You've mentioned your conclusion remains the same in this case?

A Yes. It's the conclusion that I testified to.

Q In 2004 when you published your article with Drs. Kennedy and Marchulonis didn't you state at that time that in our assessment if measles virus is detected in the gut, CSF and CNS at a time when host immune response should have removed the infection and

if the measles virus is of the vaccine strain then the potential for a persistent infection cannot be ruled out? I'll put the *D* in there.

A That's a typo.

Q Yes.

A You read it correctly.

Q Still hold that to be your opinion?

A Yes.

MR. MATANOSKI: Thank you. I have no further questions.

SPECIAL MASTER HASTINGS: Any redirect?

MS. CHIN-CAPLAN: No redirect.

SPECIAL MASTER HASTINGS: Go ahead.

SPECIAL MASTER VOWELL: Dr. Byers, you talked about the Goth article and the Agrawal article. The Goth article deals with murine dendritic cells, correct?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: And the Agrawal article deals with human dendritic cells?

THE WITNESS: That's correct.

SPECIAL MASTER VOWELL: So for purposes of opining on the affect of thimerosal on the human immune system would one study be better than the other?

THE WITNESS: Not necessarily. May I amplify a little bit?

SPECIAL MASTER VOWELL: Sure.

THE WITNESS: I think your question is whether or not there is something that is biochemically or biologically different between human and murine cells, and I do not know of any information on that. As I mentioned to you, I sit on the SBIR panel and since it's a cancer panel we get lots of cancer vaccines. It's pretty normal to be evaluating a vaccine where you treat murine dendritic cells in vitro and then inject them into the mouse.

You have to use murine because you want syngeneic, right? In the 15 years that I've been on that panel there has never been any suggestion that one cannot use the results from that experiment in order to move forward into human clinical trials.

SPECIAL MASTER VOWELL: Okay. Well, let me ask the question this way because you talked about the biphasic effect that was found on dendritic cells in --

THE WITNESS: Goth.

SPECIAL MASTER VOWELL: -- Goth, but didn't Agrawal find that thimerosal suppressed the secretion of IL6?

THE WITNESS: He said he did. If I look at one of his figures it looks to me like he enhanced it, and he is mostly focusing on I think IL5 and IL13, but these are early days. I think the main thing you should take away is the fact that there is abnormal secretion of some of these cytokines.

SPECIAL MASTER VOWELL: It doesn't matter which ones?

THE WITNESS: Basically. We're going to work this out, we're going to shake it out. The thing that I took away from the two papers is that you can have abnormalities in these key dendritic cells from nanomole amounts of mercury specifically in the form of thimerosal, and I had not gotten that before in all of these articles that I cited.

SPECIAL MASTER VOWELL: And my question is not arguing with you about which is more level. I'm trying to understand why you would have a biphasic affect in one study and why in another, and obviously one answer is one is our human cells and one are murine cells. But you don't think that makes any difference?

THE WITNESS: I really don't. I think it might just be that maybe they are measuring differently or something like that.

SPECIAL MASTER VOWELL: Okay. Thank you very much, Dr. Byers. I apologize for not asking that one earlier.

SPECIAL MASTER HASTINGS: Anything further?

(No response.)

SPECIAL MASTER HASTINGS: So from the Petitioner's standpoint we should just end for the day and start again at 9:00 a.m. with Dr. Kinsbourne. Is that correct?

MS. CHIN-CAPLAN: That's correct.

SPECIAL MASTER HASTINGS: Any housekeeping matters and anything we ought to do before we break for the day?

MS. CHIN-CAPLAN: Yes, Special Master. I thought that we had agreed that anything produced in the UK would be given to the Petitioners.

SPECIAL MASTER HASTINGS: You're talking about the expert report they got from the UK litigation?

MS. CHIN-CAPLAN: Well, apparently there was it looked like a spreadsheet that Mr. Matanoski was referring to.

SPECIAL MASTER HASTINGS: Well, I was going to ask about that myself. Our practice has been this first week of trial when people were questioning from

documents we were filing them as trial exhibits. There were three such references today that I wrote up, the letter from the Board of Allergy and Immunology, and the letter from the University of California at San Francisco and finally, some kind of document from the UK litigation.

Any problem with filing them as trial exhibits?

MR. MATANOSKI: No, sir.

SPECIAL MASTER HASTINGS: And that's what you're referring to?

MS. CHIN-CAPLAN: Right.

SPECIAL MASTER HASTINGS: All right. Well, why don't you do that. File it, and put them in sequence to the ones you filed. I think you filed the other ones already.

MR. MATANOSKI: Yes, sir. We'll do that.

SPECIAL MASTER HASTINGS: Okay. That would be good. Anything else we should discuss?

MR. MATANOSKI: Just a point of clarification. That last document was not from the UK litigation. It involves it, but it's from publicly available sources. I believe it was actually obtained by the Freedom of Information Act that the British have to obtain through those websites.

SPECIAL MASTER HASTINGS: All right. In fact, while we're on the topic -- well, we don't really need to discuss this now. Okay. Anything else we ought to discuss now?

(No response.)

SPECIAL MASTER HASTINGS: If not, we're adjourned until 9:00 a.m. tomorrow morning. Thank you, all.

(Whereupon, at 1:15 p.m., the hearing in the above-entitled matter was adjourned, to reconvene Friday, June 15, 2007, at 9:00 a.m.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 98-916V
CASE TITLE: Cedillo v. Sec., HHS
HEARING DATE: June 14, 2007
LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Court of Federal Claims.

Date: June 14, 2007

Christina Chesley
Official Reporter
Heritage Reporting Corporation
Suite 600
1220 L Street, N. W.
Washington, D. C. 20005-4018