UNITED STATES
COURT OF FEDERAL CLAIMS

COLTEN SNYDER BY AND THROUGH KATHERINE SNYDER AND JOSEPH SNYDER, HIS NATURAL GUARDIANS AND NEXT FRIENDS,	)	
Petitioners,	)	
v.	)	Docket No.: 01-162V
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

REVISED AND CORRECTED COPY

Pages: 565 through 819

Place: Orlando, Florida

Date: November 7, 2007

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UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

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SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Courtroom 56
401 W. Central Boulevard
Orlando, Florida

Wednesday,
November 7, 2007

The parties met, pursuant to notice of the Court, at 9:00 a.m.

BEFORE: HONORABLE DENISE K. VOWELL
Special Master

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C O N T E N T S

E X H I B I T S

RESPONDENT'S EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
Trial Exhibits:			
2	572	--	Slides
3	804	--	Slides

P R O C E E D I N G S

(9:00 a.m.)

THE COURT: We are back on the record in the case of Colten Snyder, Case No. 01162.

Mr. Johnson, it looks like you're leading off this morning.

MR. JOHNSON: Yes, ma'am, and the Respondent would like to call Dr. Zweiman.

THE COURT: Dr. Zweiman, would you raise your right hand?

Whereupon,

BURTON ZWEIMAN

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

THE COURT: You may be seated.

THE WITNESS: Thank you.

DIRECT EXAMINATION

BY MR. JOHNSON:

Q Good morning, Dr. Zweiman.

Would you please state and spell your name for the record?

A My name is Burton Zweiman, B-U-R-T-O-N, last name is Z-W-E-I-M-A-N.

Q And Dr. Zweiman, you are an immunologist, is that correct?

A Correct.

Q Can you describe just briefly your educational background?

A I received my undergraduate medical degrees from the University of Pennsylvania. After taking a medical residency, I took a fellowship in allergy and clinical immunology. Since 1963, I've been on the faculty of the University of Pennsylvania, School of Medicine, where I'm currently an emeritus professor of medicine and neurology. For 24 years, I was chief of the Division of Allergy and Clinical Immunology at that institution.

I also founded and helped supervise for many years the laboratory that performs autoantibody determinations in our medical center, and have done research related to that as well as neuroimmunology.

Q Are you board certified?

A Yes, in internal medicine and subspecialty of allergy and immunology as well.

Q And do you treat patients?

A I did until very recently when I'm emeritus status, but I still consult with my colleagues about patients in which the diagnosis is under consideration.

Q And are you a member of any professional

organizations?

A Yes, a number of them. I'll mention just a few. The American Association of Immunologists, the American Federation of Clinical Research, the American Academy of Allergy, Asthma and Immunology of which I was president, and a number of other immunologically-related organizations.

Q And have you received any honors or awards?

A Yes, a number of special awards from the American Academy of Allergy, Asthma and Immunology, distinguished service awards, similar to that, as well as teaching awards from my university.

MR. JOHNSON: Special Master, at this time we would offer Dr. Zweiman as an expert in the area of immunology.

THE COURT: Any objections?

MR. POWERS: No, Your Honor.

THE COURT: The Court will so accept him.

MR. JOHNSON: Thank you.

THE COURT: While we're discussing things, I noticed you have a slide up on the board. Are you going to use copies of those slides as well?

MR. JOHNSON: Yes, I'll distribute those now.

THE COURT: Okay, and these are going to be

Respondent's Trial Exhibit 2.

(The document referred to was marked for identification as Respondent's Trial Exhibit No. 2.)

BY MR. JOHNSON:

Q Dr. Zweiman, there has been some testimony in this case so far regarding autoantibodies to myelin basic protein or anti-MBP. Can you first explain to the Court what myelin is?

A Yes. As you can see in the first slide, myelin is a fatty material which coats processes that extend from neurons. These processes are called axons. The myelin coating around the axon protects it, insulates it, allows a faster induction of the electric current, if you will, that goes down, a process from one neuron to another. It also prevents the electrical charge from leaking off the process into the surrounding tissue.

Q And what is myelin basic protein?

A Well, I pushed the up button, but it didn't -- try pushing another one.

If one sees a myelinated fiber --

Q And we're now looking at slide 2 of Petitioners' Trial Exhibit 2.

A Which is shown in the upper portion of this

slide. This is the myelin sheath around an axon drawn figuratively, and the electrical current going from neuron down the axon. This myelin can be damaged in a number of ways, both on an immune basis, on an nonimmune basis, and when that happens components of the myelin, including myelin basic protein, can leak out from this area.

Myelinated fibers can sometimes be remyelinated and they are done so by a cell, a glial cell, you've heard about glial cells discussed yesterday. This particular glial cell is called the oligodendrocyte shown over here which sends out from its membrane material that becomes part of the myelin sheath on surrounding axons.

Q And we're now looking at slide 3, and you were pointing to the circle found in the middle of the slide and then the --

A That's the oligodendrocyte, and the membrane is from that becoming part of the myelin sheath that surrounds the axons.

If one looks, as you can see in the lower left-hand portion of this slide, this is a cross-section, this is the axon in the middle and then wrapped around it in concentric circles is the myelin. It's important to emphasize that myelin basic protein,

as I'll mention in a minute, is one of the major proteins present in myelin, is on the internal aspect of these layers is not so easily displayed to the outside as some other proteins that I will mention as well. It's on the internal aspect of these layers of myelin.

Q So given that background, describe what and more specifically what myelin basic protein is?

A Myelin basic protein is one of the most abundant proteins within myelin, thought to be about 30 percent of the total protein in the myelin membrane. It's thought to play a role in the formation and the maintenance of the myelin sheath. It has a very strong positive charge. The reason it's called "basic" is not because it's so simple, but because it's very alkaline. It has a very high what we call PK value.

The reason why this is important to mention is that because it is so highly charged when one tries to measure antibodies against it one has to be very careful because there is a lot of nonimmunologic findings of certain proteins to this very highly charged molecule called myelin basic protein, and one has to take care in running immuno assays that one is not just measuring an electrical attraction rather

than immunologic binding.

As I mentioned earlier, it's on the inside of the membrane, less accessible to immune attack than is myelin oligodendrocytes glyco protein, or it's abbreviated called MOG as compared to MBP which is an abbreviation for myelin basic protein.

It is one of the proteins that can leak out in the cerebral spinal fluid or occasionally gets into the blood when there is extensive myelin damage.

Q And Dr. Zweiman, you just mentioned antibodies and I was wondering if you could explain just generally how antibodies are formed?

A I think this --

Q Looking at slide -- we're skipping to slide 9.

A So most adaptive immune responses resulting in the formation of an antibody the steps look something like this. An antigen presenting cell here, abbreviated as APC, and a good example of that is a macrophage or dendritic cells will ingest the antigen, most of which are protein. They digest the antigen, break it up into what they call peptides, and present that peptide fragment of the antigen on the cell surface along with a major histocompatibility complex, which is necessary for presentation, effective

presentation of the antigen.

A helper T-cell recognizes this particular antigen by a cognate receptor which is specific for that antigen. If it stops right there, one does not get a very good immune response. Indeed, sometimes one may actually induce tolerance, but a second signal that is required in most situations is what we call costimulation, that leads to activation of the T-cell. It elaborates the cytokines which then act on another population of lymphocytes called B-lymphocytes, which are then converted into antibody-producing cells.

Q And this process that you've just described, is this process what happens when antibodies to myelin basic protein are formed?

A I believe so, yes. There is good evidence that T-cells play a very important role in the production of antibodies against myelin basic protein.

Q And, Dr. Zweiman, what is happening in the brain when there are elevated levels of anti-MBP or antibodies to myelin basic protein?

A Will this take me back? Let's see. I am going back --

Q Go back to slide 4.

A That I'm trying to do but I think I'm going to need some assistance.

Q Someone will assist you.

(Pause.)

A Yes.

Q There we go, it's slide 5. I apologize.

A This is a picture taken from a side view of an MRI study of a normal individual, and one can see the various different components of the brain, and the important thing to remember is that everything looks pretty much gray and blackened here. There are no high intensity signals.

When one has myelin destruction as shown in this side view of the brain of a patient with multiple sclerosis --

Q We're now looking at slide 6.

A One sees these high intensity, very bright white areas. These are so-called plaque areas. In multiple sclerosis from which this study was done, they tend to be concentrated particularly around spaces within the brain called the ventricle, periventricular areas right over here. This indicates areas of myelin damage, the so-called white matter of the brain is damaged. These are the plaques of multiple sclerosis.

I should mention also just for reference that it's been found that in these plaques there are

immunoglobulins, that is, Ig, that contain antibodies.

In contrast, I'm no expert in the MRI of autism, but from everything I have been told and read one does not see these areas of demyelination in the brains of individuals who have autism, even of some years duration.

Q So I take it from these slides that you've just shown that myelin damage is typically or almost always visible on an MRI?

A If one has a sufficiently sensitive one, it is seen in the large majority if not almost all individuals who have it.

Now, the question comes up could one have leakage of myelin in the absence of visible evidence of myelin damage, and that's a matter of some debate at the present time, but since one can find even in normal individuals the presence of anti-myelin antibodies in some normal individuals, one does not have to see this in every case, although one sees that's the most common pattern that one sees.

Q And I believe you mentioned earlier that you have done some research and run, I think, a lab that does antibody testing.

Have you personally tested for anti-MBP?

A Yes, we have.

Q Is that testing easy to do?

A We certainly found that it was not easy to do. We were one of the first groups in the United States to do such testing, and it required some particular laboratory manipulations and controls in order to get specific immunologic finding of anti-MBP measures.

Q And from what you have seen in your practice, are anti-MBP levels variable?

A They certainly are variable from time point to time point in individuals in which they are present. I should mention and perhaps I could mention this in one of the next slides, that anti-MBP antibodies are measured by a number of different approaches, and that's why it's difficult at times to compare findings from one report to another.

Anti-MBP antibodies of a group of antibodies against different components of the neuro or the central nervous system, they are generally by very sensitive binding techniques. By that I mean what the call Western, W-E-S-T-E-R-N, blot techniques or very sensitive ELISA, E-L-I-S-A, I believe, these are very, very sensitive and it does not necessarily prove that you have a lot of antibodies because they are so sensitive, so therefore one does not necessarily find

the same results reported by one technique as by others.

Myelin basic protein and myelin oligodendrocytes protein, nerve filament proteins have all been used as targets for measuring of these antibodies. Some groups use tissue sections of brain, either brain taken from animals, brain taken from human fetuses, occasionally from adult human brain, and therefore again that's another reason why one finds difficulty sometimes in comparing the results from one group to another.

The techniques generally are not standardized laboratory techniques. These are not like a blood sugar determination where if you had it done in 100 laboratories, probably 95 laboratories would come up with quite similar results. These are more what I call a research type technique.

Therefore, I have to look very carefully when you say the results vary from time -- they certainly are -- I didn't know whether it's the technique, whether or not it's a natural course of the antibodies in the body.

Q Doctor, are you familiar with research that suggests that elevated anti-MBP levels have been found in patients with ASDs?

A Yes, I am. Anti-MBP antibodies have been reported in the serum of patients with the ASD spectrum. The frequency of such antibodies being reported has varied reports, again possibly related to the techniques being used, as high as 50-60 percent in some series, but they have also been reported in other neurodegenerative diseases, and Connolly's group has reported present in a sizable percentage of those with epilepsy. Berger has found anti-MBP and anti-MOG in 62 percent of those with multiple sclerosis. It's been reported in normals in one series, about 25 percent of normal sera, and anti-MBP antibodies. One group was found in 50 percent for patients with active rheumatoid arthritis.

So the presence of such antibodies is certainly not specific for autism or ASD. It's not found in all patients with ASD.

Q And when you say that it's sometimes found in normals, what do you mean by normals?

A Well, individuals who -- most institutions what they use are age match individuals who are coming to donate blood, for example, and have no ostensible clinical disease of any sort.

Q So do I understand you to mean that elevated anti-MBP levels are not always a sign of neurological

dysfunction?

A That is correct.

Q Doctor, is there any relation between the MMR vaccine and anti-MBP antibodies?

A Well, let me mention one thing before I answer that question if I may.

Q Sure.

A The question that has been raised, what is the clinical relevance of finding anti-MBP antibodies, and several groups have commented on this. Most recently the group at Davis, who have been studying ASD from several aspects, whose comment in a review by Wills, et al., that they emphasize that there is no evidence that the anti-MBP antibodies are associated with pathology in ASD.

They comment that studies have not found such antibodies in the tissues in a number of cases where they have had tissues to examine in the central nervous system, and they have acknowledged the possibility that the presence of antibodies might be a marker of myelin damage due to other reasons, that it certainly is not pathogenic.

We know that taking anti-MBP antibodies and injecting them in sizable amounts into experimental animals does not by itself induce neurologic disease,

and some individuals, some authorities have even raised the possibility that the formation of anti-MBP antibodies may actually be part of a healing process.

Therefore, I think it's still an unanswered question of what the clinical relevance of the presence of anti-MBP antibodies are.

Q Okay. And then getting back to my question of whether there is any relation between anti-MBP and an MMR vaccine.

A If one speculates or postulates that the MMR vaccine in some way induces the formation of anti-MBP antibodies, one could postulate several possible reasons. One is that there might be some MBP as a contaminant in the vaccine itself, and that one is inducing an immune response to such a contaminating MBP protein. After all, the viruses are grown in tissues and one could speculate that maybe some myelin basic protein was in the culture medium, et cetera. This has been looked for extensively by several groups and no MBP has been found in vaccine.

Another possibility is that there is some sort of molecular mimicry between the measles virus proteins and myelin basic protein. Again, this has been looked at and investigated extensively, and indeed the Institute of Medicine Immunization Safety

Committee concludes that there is no evidence of molecular mimicry between these viruses and myelin basic protein.

Anti-MBP antibodies taken from individuals who have anti-measles antibodies have shown no cross-reactivity. By that I mean in individuals who have SSPE, they typically have very high levels of anti-measles virus antibodies. They also sometimes have antibodies against myelin basic protein. Yet if you take these antibodies and do what they call cross-absorption studies, there is no evidence that they're binding the same components. They are both there, but they are not cross-reacting to one another.

Bernard and his group also showed that antibodies taken from individuals with more garden variety type of measles virus infection do not cross-react with myelin basic protein.

So therefore one cannot postulate that the measles virus itself is inducing antibodies against myelin basic protein.

And the last line of evidence that I know of is that, to my knowledge, when they looked at the serum of individuals who received MMR vaccines, that this does not induce the formation of anti-MBP antibodies.

Q Doctor, are you aware of the value of the elevated anti-MBP level of 46 that Colten had in this case?

A I'm aware of it, yes.

Q Is that value sufficient evidence to conclude that Colten experienced brain inflammation or some kind of brain damage as a result of his April 23, 1998, MMR vaccination?

A No, I don't think it does. The value reported by Specialty Labs, I think it was in January of 2000, does seem quite high. It's a puzzle to me why it's so high when all the other values were not. Indeed two months after that 46 was recorded by them Dr. Singh's lab, which has, I think, been mentioned by the Petitioner on a number of occasions, did not find any evidence of anti-MBP antibodies in the serum.

The techniques were not the same, but yet it seems quite unusual to me to see what was reported at such a high level reported from the Specialty Labs and two months later to find it absent in Dr. Singh's analysis. So I think its clinical relevance is so uncertain in my mind.

Q Doctor, do you know whether Colten's CSF was ever tested for anti-MBP?

A Yes, it was in 2002, I believe, and it was

absent in the CSF that was analyzed by Singh's lab.

Q In your mind, what conclusions can you draw from that test?

A Well, the presence of antibodies against anti-MBP in the CSF would be more direct evidence of damage to the white matter or some processes causing damage to the white matter of the brain because CSF more closely reflects those local events within their axis.

I should also mention that there were no antibodies found against measles virus in that CSF specimen by Dr. Singh.

Q So just to wrap up this topic, in your opinion, in the absence of any other evidence is an elevated anti-MBP level a reliable marker for a measles infection in the brain?

A I do not think it is. One has to understand that if you're talking about a measurement in the serum or in the cerebral spinal fluid.

A And I guess in the CSF.

A Well, one generally does not obtain cerebral spinal fluid specimens unless one suspects that there is something going on in their axis, such as the rare instance of SSPE, for example. But if you're asking me in a routine measles virus infection, for example,

would one expect to see anti-MBP antibodies as a

marker of measles virus infection --

Q If that was the only evidence that you had, if the elevated anti-MBP level was the only evidence that you had, would that be sufficient to conclude that there was a measles infection of the brain?

A Oh, certainly not. No.

Q Doctor, moving on to my next topic. Dr. Bradstreet mentioned that Colten had a decreased IgA level. Do you agree with that?

A No, I do not. May I take a minute just to explain to the Court what IgA is, and what IgA deficiency is?

Much as I want to say -- maybe I should have said earlier that there is a big difference between autoimmunity and autoimmune disease, meaning that autoimmunity is not a rare event. Many of us around the room may have low levels of autoantibodies that are kept under control so that we do not develop disease.

The same thing applies to a degree with immunoglobulin A. Immunoglobulin A is a class of immunoglobulin that functions mainly by its protective effect at mucosal surfaces, that is, around the mucous membranes of the respiratory and GI tracts. When one says that an individual is IgA deficient, it means

that one has essentially no IgA. In most laboratories this is defined as levels either less than 10 or less than seven milligrams per deciliter, depending on the laboratory.

About one in every five or six hundred of us is IgA deficient. That is, we have IgA levels that are that low. Most such individuals are perfectly healthy, the findings turns out to be an incidental one that comes up because the assay was done as part of a panel for another diagnostic purpose.

When it is associated with diseases, mostly associated with an increased incidence of infections of particular types, and that is infections like chronic and persistent sinusitis, inflammation of sinuses, middle ear, pharyngitis, but talking about very frequent infections, more than the average number which commonly occur in young children, particularly if they have older siblings and particularly if the older sibling is in school, or in daycare when they bring home viruses.

The IgA deficient individual is not particularly prone to getting more typical colds than usual. It's particular types of infection.

And so in Colten's case, he had a modestly decreased serum level of IgA. It was not down in the

range that would be called IgA deficiency. Furthermore, subsequent studies done in other laboratories showed perfectly normal IgA levels in Colten. For example, one done in the University of Florida, Shands Medical Center.

Q Doctor, there has been some testimony in this case regarding the issue of immune dysregulation. As an immunologist, have you seen any evidence that Colten had a dysregulated immune system prior to his April 23, 1998, MMR vaccination?

A In my opinion, the term "immune dysregulation" has been used very loosely. It's almost as if you're watching your television news and it seems every other ad these days is for some product that purportedly boosts your immune responses, and I think that these statements are made by the people where they do not fully understand or overstate what immune responses really are.

An individual can be immunodeficient. They can be deficient in one of the major components of the immune response, and an individual can have immune-based abnormalities, but to say that such individuals have immune dysregulation without having firm evidence of it, I think is overstated.

For example, it has been stated and we heard

in this hearing that individuals who get measles vaccine are immunosuppressed. Our group, my colleagues and I were one of the first in the United States to show the immunological effects of immunization with the attenuated measles vaccine.

What happens is that one sees a moderate transient decrease in cell-mediated immunity that is expressed by delayed hypersensitivity skin testing. In our series, it was about half of the individuals exhibited this. Along with this was a decrease in cellular reactivity to certain antigens.

The humoral immune response, that is, the antibody formation to measles vaccine, the virus itself, and to other antigens was perfectly normal, and indeed Dr. Diane Griffin, an expert in immunology confirmed these findings, and extended them after we did our studies, and said very well in her testimony in the Cedillo case, which I think is on file, in which she said that one paradox is that there is this modest nonclinically relevant depression of delayed hypersensitivity cellular immunity and a very vigorous humoral immune response, including to the measles virus.

And I think the most important point is that I was able to personally observe individuals who got

the measles vaccine and exhibited decreased delayed

hypersensitivity and they were perfectly fine. There was no evidence that these individuals had more infections, or were more predisposed during the five to six weeks period of time when they exhibited this transient decrease in delayed hypersensitivity.

So one has to be very careful in differentiating what I just described seeing a much more profound decrease in cell-mediated immunity that occurs with wild measles virus infection and which has been associated with an increased predisposition to infection. In fact, as Dr. Griffin pointed out in her testimony, this is a major cause of morbidity in wild measles virus infection. That is not the situation with the attenuated measles vaccine.

Q And based on the information that you just provided, do you believe that Colten Snyder experienced any clinically significant immunosuppression either before or after his MMR vaccine?

A I saw no evidence of that.

Q There has been some testimony about an article by Dr. Weible. Do you know Dr. Weible?

A Yes.

Q Who is Dr. Weible?

A Dr. Robert Weible was a former faculty

member at the Children's Hospital of Philadelphia, well respected in pediatric infectious diseases. He is currently associated with the VICP. He was the first author in the paper to which you referred and which has been mentioned several times during this hearing.

I read Dr. Weible's paper very carefully when I was reviewing the medical records of Colten Snyder, and it didn't sound to me as if Colten Snyder's clinical presentation was similar to that as described by Weible, et al. However, I am not a pediatric infectious disease person. So I called Dr. Weible up and discussed the situation. He reviewed the clinical information and said this is not what we would describe in a group of patients that we reported.

Q And, Doctor, yesterday the Special Master asked Dr. Kinsbourne if he could identify any markers for a persistent measles infection other than a finding of measles virus RNA. Dr. Kinsbourne mentioned anti-MBP, which we have already discussed.

Can you think of a negative marker for persistent measles infection?

A Well, I first should say that I am not a measles virus expert. There will be people who are

expert in this area who can comment much better than

I. But I would like to quote a comment made by Dr. Robert Fujinami, that's F-U-J-I-N-A-M-I, who is a highly respected neurovirologist and viral immunologist, who made the point that if one is postulating persistence of a measles virus in the central nervous system of an individual, one should see evidence of an immune response against that virus, particularly within the cerebral spinal fluid.

We know that in Colten Snyder's case there was a serum immune response found in the serum a measles virus. Dr. Singh's laboratory reported that in 2002. It wasn't a huge response. Dr. Fujinami would say that with persistent infection one should expect an enhanced, very high immune response, but there was an immune response in the serum, but there was none found in the cerebral spinal fluid. And in my mind, as a nonmeasles expert, I would think that would suggest that there was not an ongoing persistence in proliferation of the vaccine measles virus in the central nervous system of Colten Snyder.

Q Okay. Just to make sure I'm understanding you, is it your testimony that the absence of antibodies to the measles virus in Colten's CSF suggest that there is not persistent measles infection in his brain?

A Well, in this regard I am trying to paraphrase what Dr. Fujinami would say in the situation. I am not an expert in that area, but that would raise that possibility in my mind.

MR. JOHNSON: Thank you very much. That's all I have.

THE COURT: You may cross.

CROSS-EXAMINATION

BY MR. POWERS:

Q Dr. Zweiman, my name is Tom Powers. I am one of the attorneys representing Colten Snyder and Petitioners in the omnibus proceeding.

My records indicate that the last expert report you filed in this matter was in April 2004. Is that accurate?

A I believe that's the last one.

Q So in the last three years, you have not submitted any other filings that are relevant to Colten's case or the omnibus proceedings as far as you know?

A I don't think I have been requested to submit anything, no.

Q In that report of April 2004, the focus of your report is responding specifically to comments made by Dr. Bradstreet, is that correct?

A That's what I was requested to do, yes.

Q And that is in fact what you did in the report in 2004, correct?

A Yes.

Q I didn't hear your answer.

A Yes.

Q Okay. At the time you prepared that expert report over three years ago, at that point was it your understanding that Dr. Bradstreet was the causation expert who would be testifying in Colten Snyder's case?

A I had no understanding one way or the other. I was just asked to respond to comments made by him. The matter of him testifying never was raised.

Q And in that expert report that you prepared, the comments that you are addressing are the autoimmunity issues that Dr. Bradstreet raised in his series of reports preceding yours, is that correct?

A Well, certainly that was the major focus of what his comments were at that time.

Q Subsequent to the filing of Drs. Kinsbourne's and Kennedy's expert reports in this case, you have not prepared any additional report for use in this proceeding, have you?

A Not to my knowledge, no.

Q You made some comments about anti-MBP. This is not in the report, so I'm not going to be referring to something specifically. In your testimony here, you mentioned the presence of anti-MBPs in what you would describe as normal people. Do you recall that testimony?

A Yes.

Q And by "normal", what you mean to say is people who are not presenting with any clinical symptoms of immune-mediated disease?

A As best I can tell from the papers that I have read, these were normal controls, normal healthy individuals.

Q And normal, I'm just trying to get to what normal means. If there are anti-MBPs found in those people, the definition of normalcy is based, if you know, on the presentation of clinical symptoms or the lack of clinical symptoms?

A I cannot speak for the authors of those reports exactly how they chose the normal controls, but I can tell you what most scientific studies that are well carried out, they use as normal controls people who are coming in to donate blood, in the case of children, there are pounds of sera obtained from well children visits, things like that, are used as

normal controls.

Q And all I am trying to get to is a normal control would be an assessment that's made in the clinical presentation because if they found anti-MBPs and the presumption is that the normal would have none, it sounds like somebody who had anti-MBPs, if that was the definition of normal, would not be normal?

A I think your reasoning is circular. A normal individual is one who in scientific studies the individual is clinically normal. If you find a particular immunologic finding, that does not make them abnormal. It means that that finding is present in some normal individuals.

Let me emphasize for the Court that an antibody assay is not a black or white situation, particularly with these very sensitive binding techniques. I'll give you a concrete example.

A disease called systemic lupus, that is characterized by the presence of anti-nuclear antibodies. It's a very sensitive technique the way our laboratories do it these days. But because of that, it is not unusual to find such antibodies present in a one to 40 dilution of serum from normal individuals, maybe 40 or 50 percent of normal individuals will have that antibody present in the one

to 40 dilution of the serum.

So one has to go out to either one to 80 or one to 160 dilution before you get a cutoff between that found in normal individuals and that found in patients with systemic lupus, and the same thing applies when one talks about the anti-MBP antibodies. Dr. Sinclair, who is frequently quoted by the Petitioners, what they do is they find it in plenty of normal individuals, but if they dilute out serum far enough they find they can find a distinction between their study population and others, and other groups have found that they can dilute out the serum and find it in normal individuals.

So it's not is it there or not, it's how much you have in there, and with the Western blot techniques used by a number of laboratories, it is not a quantitative measure. It's more of a semi-quantitative measure of whether how much is there.

So when you say to me does the presence of anti-MBP mean that somebody is abnormal, the answer is it depends. If the individual is clinically normal, it's normal.

Q And actually the original question was much simpler, which is that when you use the term "normal", did it refer to clinically normal. It sounds like the answer to that question is yes --

A That's what --

Q -- it's clinically normal?

A That's what all the clinical studies have done.

Q All right.

A Is clinically normally control. Now, there are other control populations, but clinically normal.

Q Right. Yes, and that's all that I was asking.

Now, if there are MBPs in samples taken from clinically normal people, the anti-MBPs would have to come from somewhere, is that correct?

A In the first place, it's not MBPs. You said if the MBPs are normal.

Q Anti.

A Oh, anti-MBP.

Q If I did say, that's what I meant to say and that's what I thought you said, but yes, if you have anti-MBPs that are present in normals, those would have to come from somewhere, isn't that right?

A If one gets around the technical aspects, there are nonimmune binding of immunoglobulin to this highly charged molecule called MBP. It would be present in serum from normal -- it has to be made. The reason for it being made is not clear.

Q And the reason for their being made in your slides was that because of the damage to the myelin sheath?

A That is the most likely situation one finds. I'm not saying that's the only one.

Q Understood. So if you have anti-MBPs found in a clinically normal person, it still does suggest --

A Anti-MBPs. You keep saying MBPs.

Q Yes. If you have the presence of anti-MBPs in samples from clinically normal people, it would strongly suggest that even in those clinically normal people there has been damage to the myelin sheath?

A No.

Q What would it suggest then? Where would these anti-MBPs come from?

A I just said that damage to the myelin sheath is the most common reasons, but I didn't say it was the only thing that could happen.

Q Well, I will ask in a second what other sources there could be, but would it be fair to say that if not exclusive, if the presence of anti-MBPs in normals is not exclusively derived from the damage of the myelin sheath, it would be consistent with myelin sheath damage. Is that a fairer statement?

A I would want to see other evidence that

there was demyelination before I conclude that this was indicative of myelin sheath damage.

Q What kind of evidence would you look for?

A Well, one is highly sensitive MRI, the evidence of demyelination just as I have showed you seen in multiple sclerosis and found in some other demyelination disorders. Some groups actually measure the MBP in the spinal fluid as a measure of myelin damage. This is done by some groups to follow multiple sclerosis patients.

Q And let me interrupt you for just a second on the MRI response. You're talking about very sensitive MRIs. Are you aware of MRI imaging of peoples' brains who were clinically normal that show the type of myelin damage that you would see in say a multiple sclerosis patient with plaques?

A No. That's the reason why I concluded that evidence of myelin damage is the most likely scenario, but not the only one in which one can see evidence of anti-MBP antibodies.

Q Okay. I understand, but the question was are you aware of say peer review-published studies where MRI imaging was done of the brains of clinically normal people that found evidence of myelin damage similar to what you would find in multiple sclerosis?

A Not in taking a population of normals, but it's been --

but one can get areas of demyelination without showing up on the MRI without having evidence of clinical manifestations to go along with that.

A classic example is in multiple sclerosis where an individual will present with an acute episode frequently involving the eye, and when they do an MRI, they find a area of demyelination that corresponds with the clinical symptoms at that time because they find an older area in another part of the brain that was made six months or a year earlier, at which time the individual had no symptoms. It's one of the things they have learned about multiple sclerosis. You can get these asymptomatic involvement areas.

So it's conceivable, to answer your question, that an individual at that time may have had some disease. So I think that two parts answer your question. One says in that scenario just as I described it, but there may be other reasons why you can have a stimulus to the production of anti-MBP antibodies. I think my final conclusion would be the same. The clinical relevance of it in some individuals is still uncertain.

Q On slide 8, if you could -- I don't have the numbers in front of me, but if you could -

//

A What's the title of that one, please?

Q The title of slide 8 is "Antibodies Against Myelin Basic Protein."

In that slide you referred -- it's on a slide, you mentioned it in your direct testimony, the finding that antibodies against myelin basic protein are found in the serum, blood serum in several disorders, including in epilepsy, correct?

A Dr. Connolly's group has found it in epilepsy, yes.

Q And understanding that you're not putting yourself out as an expert in autism spectrum disorders, do you have any information that would allow you to conclude that the incidence of epilepsy among autistics is higher than the incidence of epilepsy among nonautistics?

A I'm not an expert enough to say definitively, but I should tell you that Dr. Connolly and her colleagues specifically in that report emphasized that these bases for epilepsy were looked carefully for evidence of ASD and found not to be present. These are individuals in which there was no evidence of ASD, according to them, and I gather that her group is respected for their studies in this area.

Q You also mentioned the possibility that the

presence of anti-MBP might be evidence of what you

describe as a healing process. Do you remember that statement?

A Yes. That's not my is a hypothesis or postulate. Some authors have described that as a possibility, that that might be part of it. I don't know if they have firm evidence for it. I pointed that out only to say that there is still considerable uncertainty about the pathophysiologic significance of anti-MBP antibodies.

Q Sure, but my question is going to be relatively simple, I think, by this idea that it might be part of the healing process, at least to me raises the question healing from what. Do you have any sense of what those authors or other authors or yourself would think that a person who was demonstrating the presence of anti-MBPs as a healing process, what they are healing from?

A Well, again, I don't want to speculate what these authors intended when they made those statements. I could say that I can give you a possible scenario, and that is that if we found in some what they call white matters strokes, that there are in some individuals increased levels of anti-MBP antibodies.

I had mentioned earlier that there is

attempt at remyelination, not always successful in

individuals with new myelin layed down by the oligodendrocytes, and that could be part of the anti-healing process, remembering that the -- what I said earlier that MBP is not externally displayed on coils of myelin. It's internally on a cytoplasmic aspect of the coils of myelin. So it may be that when you are laying down new myelin maybe you expose it. This is all speculation on my part.

Q And I understand that. I appreciate the fact that you're allowing for the uncertainty of what might be going on here.

The question though comes back to if new myelin is being laid down, if myelin sheath is being reconstructed in the brain, one would need to assume that something damaged or destroyed the myelin in the first place in order to initiate or requiring a healing process. Isn't that correct?

A I would assume so.

Q So something would have had to happen in the brain for these anti-MBPs to be present somehow?

A I'm not sure exactly where you're going with the question, but if you're trying to imply that there is some myelin damage that initiated this response, I'll have to defer to those like Dr. Wiznitzer who knows a lot more than I do about the neuropathology of

ASD.

But my understanding is that myelin damage has not been an impressive finding in the limited number of, you know, autopsy or other pathologic sources of information about the abnormalities in ASD.

Q Yes, and I wasn't even speaking specifically of ASD. It was just the curiosity of whether if you have, again, evidence of anti-MBPs, there are at least postulates that might be part of the healing process --

A I should tell you before I --

Q Please let me -- I will have a question. But if you have evidence of anti-MBP production in the body and you've explained that that's a result of damage to the myelin sheath, so some people have said it might be part of the healing process, my question I think is relatively simple. Doesn't that require that some sort of damage to myelin must have occurred at some point? And I'm not asking you to limit it to a particular cause, but doesn't it mean there has to have been some damage to myelin in the brain?

A No, because I said at the very beginning that myelin damage appears to be the most common one would describe, but not the only one, and I'll give you a concrete example of that.

Q And again, let me -- you answered the question. Allow me then to narrow that question. I said would it necessarily mean. Based on your answer, it's the most common. So it is more likely than not that --

A I'll give you a scientific answer. I'll not give you a legal one.

Q Well, actually when you say "common" --

A No, it --

Q Explain to me what you mean by it's the most common reason.

A I'll give you an example of where it's not. One group has reported that when they find anti-MBP antibodies, this is highly suggestive that it's due to homology with certain bacteria chlamydia for example, and even they found homology in those cases with serum reacting against cow's milk components. Maybe that's the stimulus for the production of anti-MBP antibodies. It has nothing to do with myelin destruction, and that's a record, I think, that's been filed in this case.

MR. POWERS: It has. Well, I don't have any further questions but before I step down, Special Master, I do want to note one thing that I am a little troubled by. The presentation of this witness is

based on your prehearing order that made it clear that witnesses who will be testifying as experts must

identify ahead of time issues, arguments and citations they would be relying on.

There are a couple of points in here with a discussion about the -- referring to whether the Weible article or Fujinami that haven't -- are now being put into the record here. So I just want to raise it as a flag here that I hope that Respondent's experts are not going to be put up here to be talking about things that would be precluded by your prehearing order, and I think we bumped up really close against that line on this direct.

THE COURT: I'm not following you. My prehearing order was designed to ask the parties to call to my attention articles that had been filed but that had not been referenced in particular expert reports. I think the Fujinami article had actually been filed in Cedillo, and then refiled here. But the new article is here.

In other words, don't give me a list of 150 new articles without having a reference to them in the expert's opinion or something else that you filed to tell me why it's significant.

MR. POWERS: So just because you have an expert report three years ago citing articles to then be pulling in phone conversations and things like that

to sort of bolster those articles, I know the Rules of Evidence don't apply, but I just raise that as an issue of concern that expert testimony be within the scope of the materials that have been filed, and the reports that have been filed.

THE WITNESS: Special Master, may I respond to that?

THE COURT: I would be happy to hear what you have to say, Doctor.

THE WITNESS: Thank you. In the first place, so far as the Weible article, I filed that as part of my report, and the reason why I mentioned my telephone conversation with Dr. Weible is that the Petitioner has repeatedly raised the Weible report as an example where Colten Snyder's case would fit in within the framework of that report, and I thought it would be helpful to the Court to give the comments of the first author of that report about whether or not this was similar or not.

Now, if that went beyond the bounds, I don't know, but I'm just saying that's the truth as I know.

THE COURT: Well, and I know the Weible report was also cited by Dr. Ward and discussed by him.

No, I don't consider it to be out of bounds

particularly given that we've had considerable discussion of that report. My concern is that I do not want to have happen in this case what happened in Cedillo, at the last day, the last hour of the last day of trial we're handed a medical journal article that no one had ever seen before, and witnesses are being asked to comment on it.

I do not want trial by ambush. So if an article has been referred to or discussed by a witness, whether on the stand or in an expert report, that is, your witness discusses the Weible article even if Dr. Zweiman had not previously mentioned it, he would be free to discuss that article as well if his understanding of it were different from that of another witness.

What I did not want is somebody dumping textbooks of 18 or 20 inches a part and citing the textbook merely and not telling me what part -- or anyone else -- what part of that textbook supported their opinion, nor did I want people attaching 20 or 30 or 40 articles to an expert opinion citing only six of them in the opinion, and then expecting to walk into the courtroom and all of us having read the other 40. I like to read the articles before the witnesses testify about them so I have an understanding of

whether their testimony matches up with my reading of the article, and so that's where we stand.

I have certainly read and digested the Weible article. I asked questions about it yesterday. So Weible is certainly fair game.

If we get to something that's been out there that nobody has mentioned but suddenly becomes the crucial article in the case, and if that is the intention of anyone out there, bring it to our attention now. No trial by ambush.

It's very difficult for me then to have to go back and read the article and not have any experts I can ask questions about it to ensure that my understanding comports with that of the people who are trained in that field. Clear?

Don't get me wrong, Mr. Powers. I appreciate your raising the concern, but that was not what I intended by the pretrial order, to say that if you are going to file new stuff reference it, talk about it. Don't just give me a stack of articles to show how learned you are.

MR. POWERS: Or how much access you have to Medline.

THE COURT: Exactly. We get bottomless accounts.

All right, I have a couple of questions for you, Dr. Zweiman. They are not particularly tricky or difficult. They are just to ensure that I understand what we're talking about.

As I hear your testimony you are saying the 46 finding of anti-myelin basic protein in Colten appears to you to have no particular significance.

THE WITNESS: I would use the term of uncertain significance.

THE COURT: Okay.

THE WITNESS: And it's very puzzling to me in view of the fact that the serum obtained two months later was completely negative, and subsequent analyses have shown that the levels where he was slightly elevated or were normal. Both run in the same laboratory that obtained the 46 value.

THE COURT: Okay.

THE WITNESS: To say something happened clinically that were different, certainly the one from two months later, at least in my perusal of the record it was hard for me to distinguish if things had changed that dramatically, so I'm not sure what that 46 meant.

THE COURT: Well, we have the first finding of 46 anti-myelin basic protein antibodies to myelin

basic protein in January of 2000.

THE WITNESS: Correct.

THE COURT: Several months later Colten begins IVIG treatments.

THE WITNESS: I was told, and I stand to be corrected if I'm wrong, that that serum that was sent to Dr. Singh was obtained before the IVIG.

THE COURT: Correct. Correct. The original serum -- let me go back to see if I can find something set off for Dr. Singh.

THE WITNESS: I don't have a copy of the timeline that was sent out.

THE COURT: And I'm not sure that it will list everything on the timeline.

Okay, let's start this way. There is a serum sample drawn on 3-8-00 that is sent to Dr. Singh.

THE WITNESS: Right.

THE COURT: And that would be Petitioners' Exhibit 207, page 1. Unfortunately, those were some of the labs that didn't make it into my chart. So that may have been taken again at the same time.

THE WITNESS: That was --

THE COURT: At the beginning of the IVIG. Then there are subsequent IVIG tests -- excuse me -- subsequent IVIG administration and subsequent myelin

basic protein results which tend to be negative or low range. I think there is one that's isolated at 14.

So what would happen then if this specimen is in fact taken before the administration of IVIG? Why did we have a drop from 46 to negative in a period of two or three months?

THE WITNESS: The difference between January result of 46 from Specialty Labs and the negative results of Dr. Singh's lab being the specimen of March 8th, is a puzzlement.

There was, as best as I could tell, nothing going on therapeutically in that interval that would have converted an otherwise strong positive to a negative result.

THE COURT: Would Secretin in --

THE WITNESS: I don't think that would.

THE COURT: Okay.

THE WITNESS: If you're asking me does IVIG therapy, would that convert a laboratory test, one aspect I already alluded to and that is that one has to know when to draw a blood specimen and that should be at least three to four weeks after the last IVIG administration to avoid any artifactual effects on it.

I cannot tell you how the timing was of those specimens, and the IVIG administration. So I

cannot comment about that.

THE COURT: Well, let me ask a question this way then. Would you expect that IVIG would be an appropriate therapy to treat MBP antibody level that was high?

THE WITNESS: No, it is not -- in the first place, I should say, that, and this may not be exactly an answer to your question -- that the recent consensus report, and I'm not trying to throw something new to you, but this just came out, the recent consensus report from a group of experts in Canada about indications for the treatment of neurologic disease with intravenous IG did not recommend the use of IVIG in autism.

In direct answer to your question would I use IVIG to decrease the level of anti-MBP antibodies, I would not use that as a marker of whether I'm going to use IVIG therapy or not.

The measurement of particularly anti-MOG antibodies is recently reported as a possible indication for other types of treatment of multiple sclerosis, but it did not mention intravenous IG therapy.

THE COURT: How long does it take, let's say after an event that might trigger the production of

anti-myelin basic protein antibodies to having those

antibodies show up in blood or CSF?

THE WITNESS: It's difficult to say with certainty because there has not been systematic sequential studies, but my supposition based on what I have read is within say two to three weeks, something like that.

THE COURT: Okay. And once elevated, do MBPs stay elevated or are they cyclical?

THE WITNESS: They are variable, remembering that when you measure the serum you're measuring it, if you will, in some distance, anatomic distance from where the presumed action if you're postulating it's some event in the central nervous system. You have heard from others that there is a blood brain or blood CNS barrier that keeps the plasma protein systemic compartment away from the compartment within the nervous system so that, if you will, what you're measuring in the serum is coming sort of indirectly from what is coming say from the nervous system.

So that it's not surprising that one could find variable levels of anti-MBP antibodies. It's not a constant from week to wwek and from month to month.

THE COURT: So I take it from your testimony, Doctor, that you don't consider that there is any treatment necessary for an elevated myelin

basic protein and that it is not a marker for guiding other treatment?

THE WITNESS: By itself, if that was the only thing that was present, it certainly in my opinion would not warrant treatment for that.

I mentioned a few minutes ago in certain settings there is suggestive evidence that the presence of an anti-MBP, and particularly anti-MOG, that's a myelin oligodendrocytes protein antibodies, it might be a marker of potential problem in multiple sclerosis. There is a recent report in the New England Journal of Medicine that pointed that out as a possibility.

But just to use anti-MBP as an indication of treatment would not be warranted, in my opinion.

THE COURT: Did any of Colten's tests suggest to you that he had a serious immune deficiency, and if so, when?

THE WITNESS: I did not see any evidence that he had a serious immune deficiency as evidenced by either the pattern or severity or frequency of bacterial infections, or unusual infections.

I should mention, by the way, if this is helpful, that in wild virus, wild measles virus infection the suppression of immunity is mainly

directed against cell-mediated immunity, not antibody production immunity. I believe I alluded to that earlier.

Dr. Diane Griffin described it very well in her testimony in the Cedillo case, and as I told with the individuals who get the measles vaccine, in our experience these people were perfectly healthy, had no increased incidence of infections during the time when there was a decrease in their delay in hypersensitivity with cell-mediated immunity.

THE COURT: There are medical tests that show Colten had an elevated IgE levels several times. What does that tell you?

THE WITNESS: As I commented in one of my reports, there was a single determination and a very high level, although some individuals have reported increased serum IgE in some individuals who have ASD. The levels reported here are strikingly elevated, and I commented in my report that this appears to have not been followed up on but that was certainly warranted because in the absence of any skin manifestations of a topic dermatitis or other reason for the IgE being so high one would want to make sure that the child did not have a parasitic infection that could be responsible possibly for chronic diarrhea that was

described in his case.

However, I did not see results of a repeat serum IgE. This does not mean that he was immunodeficient. There is a condition called hyper, H-Y-P-E-R, IgE syndrome, or some people call it the JOB's, J-O-B apostrophe S, syndrome named after the figure in the Bible, but these individuals have a particular pattern of infection which was not present in Colten, and therefore I think it's unlikely that that is a reason for the quite elevated IgE level in this case. But I think the first step would be obviously to have it repeated the test repeated.

THE COURT: So that's what you would expect a doctor who got those serum results to do?

THE WITNESS: I do. If I had seen that, I certainly would have had it repeated.

THE COURT: All right. After repeating it if it's still high, what would you do?

THE WITNESS: Investigate for parasitic infection, number one. The child had, and I may be going yet beyond the bounds of my expertise, but what was commented yesterday about the reports on intestinal biopsy, the child had, it sounds like impressive numbers, and I would want to have an experienced pathologist look at that, but there is a

condition called -- I have to spell this one out -- eosinophilic gastroenteritis. It's E-O-S-I-N-O-P-H-I-L-I-C, gastroenteritis, a condition characterized by increased collections of the eosinophils in the mucus membranes, in various parts of the intestinal tract, and there is a sizable percentage of these children who have reported allergies to foods or foods to induce GI manifestations, which appears to be the case in Colten's case, and some of those individuals have pretty impressively elevated serum IgE levels. So that's another condition that would have to be looked at.

So there are others less likely but those are the ones that would come to mind.

THE COURT: Mr. Johnson.

MR. JOHNSON: Just a few. Thank you.

REDIRECT EXAMINATION

BY MR. JOHNSON:

Q Dr. Zweiman, going back to the issue of IVIG and its potential effects on anti-MBP levels. I think you mentioned that the administration of IVIG through a dilution process may have some effect on lowering anti-MBP levels. Did I understand that correctly?

A If a specimen is obtained within three to four weeks after the IVIG administration, obviously

depending what dose of IVIG used, but I'm making assumptions that it's a sizable dose of IVIG.

Q So knowing that, if you're going to take a serum sample and send it for testing for anti-MBP levels, it wouldn't make sense to do that following the administration of IVIG, you would want to do that beforehand, is that accurate?

A Well, before and after for an individual who is getting IVIG on a regular basis. What the usual practice is in people who use IVIG therapy on is if they do an assay, a serum marker of the disease, or in the case of immunodeficient to measure total IVIG levels, you always obtain a specimen at least three or four weeks after the last infusion, and it's typically done right as you're putting the needle in to administer the IVIG. You get a serum specimen at that time, a blood specimen, and then hook up the IVIG therapy.

Q And you do that because you're trying to get the most accurate reading?

A You're trying to get what is the reflection of the person's own biology.

Q Okay.

A And not donated by or affected by the IG that's being administered.

Q So, for example, March 8th of 2000, when

Colten had not had any IVIG up to that point, if a sample were taken, as you said, that would be a reflection of Colten's actual anti-MBP levels?

A What's going on -- what's going on in his own body.

Q And then again just as an example, the records indicate that, and this is at Petitioners' Exhibit 12, pages 41 to 42, that he had IVIG on June 11th of 2001, and then at Petitioners' Exhibit 12/473 through 477, it appears that his next IVIG treatment was on August 6th of 2001, and apparently that same day there was a sample taken to the Specialty Labs. This is at Petitioners' Exhibit 12, page 461.

Given the span of time between June 11th and August 6th, is that an appropriate amount of time to be taking a sample and to have that indicate what the person's anti-MBP production would be?

A I would think so. I'm making the assumption that the blood specimen was obtained right before they gave the IVIG therapy.

Q And that would make sense to do that.

A That's the way it's usually done.

Q And so if the value for that day were four, in your opinion that would indicate what Colten's normal anti-MBP production was at that time?

A Four you said?

Q Four, yes.

A Yes. That would seem to be a measure of what his own body was doing.

Q And, Doctor, you've sat through the testimony this week, haven't you?

A Yes.

Q And you heard Dr. Kinsbourne testify. Is it your understanding that his specialty is pediatric neurology?

A That's what I have been told.

Q And Dr. Kennedy, his specialty is -- he was brought in as a virologist. Is that your understanding?

A That's what I understand.

Q And so based on that, is it your understanding that given they submitted reports after your last report, that there may have been other experts who responded that were more appropriate to respond to what they included in their report?

A I'm not sure I understand what you mean.

Q I'm sorry. I asked the question very poorly.

I guess what I'm asking is since you are not a virologist or a pediatric neurologist, is it your

understanding that there may have been other people that Respondent is working with that were more qualified to respond to the reports of Dr. Kennedy and Dr. Kinsbourne?

A Oh, for sure.

MR. JOHNSON: Thank you.

THE COURT: Go ahead, Mr. Powers.

MR. POWERS: If I could, Special Master, just based on your questions could I --

THE COURT: Sure.

MR. POWERS: I think it's just one question.

THE COURT: Sure.

RECROSS-EXAMINATION

BY MR. POWERS:

Q Doctor, you may recall when the Special Master was asking questions she asked you about the time between an event that would cause the production of anti-MBPs and the appearance of the anti-MBP in serum or --

A Cerebral spinal fluid.

Q Or CSF. I wanted to make sure I --

A You said the appearance or the production of?

Q Well, my understanding of the question was there is an event that produces the anti-MBPs and then

there is some point later in time where they can be

detected. Is that a fair restatement of the question?

THE COURT: It is.

THE WITNESS: I may have misstated it. I thought you meant when does one seeing production of the anti-MBP response, and that would be within several weeks, I believe, maybe somewhat longer before one sees appearance of that in CSF/serum.

THE COURT: And detectible levels?

THE WITNESS: Detectible levels except in the serum, it might be several weeks after that because of some of the factors I mentioned. You have a point source of production of it, and the fusion away from that area, so it might be -- this is speculation on my part because I have not studied this myself, but you know, it could be up to six weeks, something like that.

BY MR. POWERS:

Q And that's why I was asking the question, because the answer was two to three weeks for detecting it on a test.

A I said I thought you meant when you start seeing production of the immune response.

Q So it would be two to three weeks before one would see production of the immune response, and then another two to three weeks before it would arise to

the technical levels.

A I can't give you exact because I have not studied it myself, but that's what I would think. I would speculate on that.

Q And then a quick follow up to that on the detection portion of it, estimating a timeframe for detecting something, is that based on what we know about the process of anti-MBP production or is it based on the technology and the sensitivity or the type of tests that would be used to detect it?

In other words, are there different tests that you would use that are going to produce different results? Some are more sensitive?

A Well, there are certainly some tests that are more sensitive than others. If you are referring to the testing that was done in Colten Snyder's case, the technology that was used, you know, I wasn't there when the test was done, but you know, I read the description of what they did, and one was by Western blot and the other was by ELISA technology.

It's a cumulative matter of when one would see it. If one got over a period of some time -- just for example when you're immunized you start detecting low levels of antibody and then the levels of antibody go up even though using the same technology over to measure the time, and it takes -- what I was referring

to was that I would speculate that, you know, up to six weeks you would start getting because there's increased production of it one would expect to see increased levels, and it may not be to the level of detection until maybe out to five-six weeks, something like that.

MR. POWERS: That is all I have.

THE COURT: Okay. Anything further for Dr. Zweiman?

MR. JOHNSON: Nothing from Respondent.

THE COURT: Dr. Zweiman, thank you. You may be excused.

(Witness excused.)

THE COURT: It's now about 10:25 or so. Do we want to make our midmorning break or do we want to push on?

MR. JOHNSON: Let's take a break if you don't mind.

THE COURT: Okay. Fifteen minutes, we will reconvene then, make it easy, at five to.

(Whereupon, a short recess was taken.)

THE COURT: We're back on the record in the Snyder case.

Mr. Johnson, your next witness is on the stand?

MR. JOHNSON: Yes. Respondent has called Dr. Wiznitzer.

THE COURT: Would you raise your right hand, Dr. Wiznitzer?

Whereupon,

MAX WIZNITZER

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

THE COURT: Thank you.

DIRECT EXAMINATION

BY MR. JOHNSON:

Q Doctor, please state and spell your name.

A Max Wiznitzer, W-I-Z-N-I-T-Z-E-R.

Q And you testified at the Cedillo hearing, is that correct?

A Yes, I did.

Q So we will not go through your credentialsad nauseum, but if you would just refresh the Court's memory as to where you are currently working?

A I am working at Rainbow Babies and Children's Hospital in Cleveland, Ohio, as a staff neurologist. I am also an associate professor of pediatric neurology at the International Health Education at Case Western University in Cleveland, Ohio.

Q And you do have a clinical practice, is that correct?

A Yes, I do.

Q And you treat patients that have autism or other ASDs?

A Yes, I do.

Q Approximately what percentage of your practice is dedicated to the treatment of patients with ASD?

A Up to 25 percent.

Q And is that a self-imposed number or could you treat more ADC patients if you wanted to?

A The answer is yes, it is a self-imposed number, and number two, I could easily have a practice made up 100 percent ASD children if I wish.

Q And the reason that you limited yourself to 25 percent is?

A There is a demand for my services in other areas, and also because I'm a child neurologist and I want to make sure I maintain my skills in child neurology.

Q Doctor, you have sat through the testimony that Petitioners have presented during the trial this week, is that correct?

A Yes, I have.

Q Did you hear anything that was presented

this week that would change your opinion regarding whether the receipt of an MMR vaccination combined with the administration of Thimerosal containing vaccine more likely than not causes any disorder that is on the autistic spectrum?

A No, I have not heard anything to change my opinion.

Q And just for the record, what is your opinion on that issue?

A My opinion is that the vaccines do not cause autism or ASD.

Q The hypothesis that Dr. Kinsbourne described yesterday during his testimony, in your opinion was that essentially the same hypothesis that he described at the Cedillo hearing?

A Yes, it was.

Q Have you seen any new evidence since you testified in June at the Cedillo trial that Dr. Kinsbourne's hypothesis has gained any new support in the medical community?

A No, I have not.

Q And do you still hold all of the opinions that you expressed on the issue of general causation at the Cedillo hearing to a reasonable degree of scientific probability?

A Yes, I do.

Q Doctor, then I would like to turn to the specific facts of the case involving Colten Snyder, the Petitioner at issue here.

In your opinion, did Colten Snyder's April 23, 1998, MMR vaccination cause him to develop ASD?

A No, it did not.

Q Does the evidence in this case support a finding that Colten suffered an encephalopathy as the result of his MMR vaccination?

A The evidence does not support that conclusion.

Q Doctor, have you seen a wild measles infection?

A Yes, I have.

Q So I assume that you know then what the clinical picture of a measles infection looks like?

A Yes.

Q Based on your review of the records, do the records describe the symptoms in Colten Snyder that are consistent with a measles infection?

A No, they do not.

Q And I believe that Dr. Kinsbourne testified on his cross-examination that he saw evidence that Colten may have experienced some other types of

infections following his MMR vaccination. Do you

agree with that?

A Yes, he did.

Q Doctor Kinsbourne, during his examination yesterday, talked about lethargy as one of the first signs of autism that he noted. Do you agree with Dr. Kinsbourne's assessment on the issue of lethargy?

A No. May I explain?

Q Please do.

A Dr. Kinsbourne represented to the Court, and I'm going to paraphrase his words, that in his opinion the description of lethargy as given over the Memorial Day weekend in 1998 -- it may have been at least the Monday of Memorial Day, then the following day, the Tuesday is when I think it was when Colten Snyder was actually admitted to the hospital -- that there was a description of Colten Snyder being lethargic, and Dr. Kinsbourne stated that lethargy could be a misinterpretation of the beginning of the social withdrawal or the inward in-turning as the words that he used to describe the social behavior of a child with autism.

However, the formal definition of lethargy and I'm quite familiar with it because when we do EEGs, which I do on a weekly basis, that's one of our diagnostic codes that we use within the EEG reading,

the formal definition of lethargy is actually an impairment in consciousness. In other words, you're not fully alert and awake. Lethargy means that there is a mild diminution or decrease in your level of consciousness, but you're still able to be aroused. You're still able to be responsive, but if I leave you alone, you will go back down to that decreased level of consciousness.

By definition, a decreased level of consciousness is not part of the diagnostic criteria of any autistic spectrum disorder. In fact, if there were an impairment in consciousness in a child, we would be looking for alternate diagnoses. Therefore, the use of the word "lethargy" to define the social behavior of a child with autism is not really the appropriate word to use.

Q Based on what was going on with Colten at the time, is there in your mind a more likely explanation for the cause of his lethargy?

A Yes, there is.

Q What is that?

A The medical records tell us that he clearly had a viral illness, and the medical records also document that he showed clinical evidence of dehydration, the description that was given there, and

one of the things we know is that when he was put in the hospital he was given IV hydration. He was discharged, he was described as awake, and obviously, you can't be awake and lethargic at the same time which means at that point there was a significant improvement in his level of consciousness, back to the level that you would expect it to be, otherwise he wouldn't have been discharged from the hospital, and that is inconsistent with the behavior that you would see of the social changes, the social behavior in autism where once it starts it will become clinically evident. It doesn't go away in two days.

Q Doctor, we have already talked about the Weibel article a little bit this morning, and how that has been used in support by Petitioners to support the idea that Colten somehow fit the framework that's outlined in the Weibel article.

Have you had an opportunity to review the Weibel article?

A Yes, I have.

Q And can you just describe your understanding of the framework that's set out in the Weibel article?

A If you will just give me one second because I know I have it in here.

(Pause.)

Basically the framework that was used was taking information that was reported to the VAERS system and basically one of the criterion they looked at features of encephalopathy, ataxia, seizures. They looked at the children, but they had exclusionary criteria in that paper, and if you read the methods section the exclusionary criteria was that the authors did not accept a case if there was an alternate explanation for the features that were present at that time.

Clearly in Colten Snyder's case the events that occurred around Memorial Day of 1998, the medical records tell us that there is an alternate explanation. He had an acute viral infection with fever with pharyngitis, and with dehydration, and basically when he was treated he improved. This is not a case that would have been accepted within the criteria as defined in that paper.

Q Doctor, there have been a number of videos that have been provided by the Snyder family. Have you had an opportunity to review those videos?

A Yes, I have.

Q Can you just describe generally for the record what is on those videos?

A What was provided to me was videos of Colten

Snyder, and of course we also have other members of his family, starting at age three weeks to age 13 months. Then there is a gap in the records, and then the video resumes, the initial portions of the video resumed, as described according to the given timeline that was presented with the video, or after the video was given, a chronology was finally provided of autumn '99, and actually some information that was stated to have been from February or March of 1999, and basically running up to about the time of his third birthday.

Q And did you review all of the videos that were provided by the Petitioners?

A Yes, I did.

Q Based on the videos and of course other materials, medical records that you've reviewed in this case, do you agree that Colten showed signs of developmental delays?

A Yes, I do.

Q Just tell us generally what your impression from watching the videos was.

A From the limited information I had on the video, but it's a recurrent thing, in other words it's something that doesn't change, what becomes obvious in the video is the decrease in expected language use up

to age 13 months. When one basically watched Colten Snyder in action during this time period either he doesn't make any sounds, he screeches, he makes some nonspecific noises, and he extremely rarely says either ba, ma, or maybe a two-syllable sound like a baba or mama, but it's not a lot. There is no interpersonal babbling that I can see.

In other words, there is plenty of opportunities, his siblings come up and talk to him, he doesn't talk back to them in the way a baby would. He doesn't seem to sustain any kind of a language interaction that's there, and what's most impressive to me -- actually one of the points that's impressive to me on the video is that we have the opportunity to have a - if you want to thin of it as a control, and if I may identify, there is a portion of the video when he is seven months old where there is another child going around his playpen, basically babbling, and it's not Colten, because when we look at Colten, you watch his mouth, it's not moving, and I played that section back multiple times, but there is another baby who is basically making a lot of baby noises around there, and this is not the behavior that Colten manifests anytime in the video, whether it's at seven months, whether it's at 11 months, which is Christmas

time, whether it's at 13 months when we're taping him here.

He looks at the camera, he plays with the camera lens cover multiple times. He has inconsistent responses to voice. Sometimes when he was called he responds, sometimes he doesn't, and what I take from that, because I also have evidence afterwards of his language that's given to us, and just for people to reference things, and I will reference the points for you, the one at seven months is basically on what's called Title 6 on the video, and it's part of what's called Chapter 2 if anyone wishes to look at that, but later on when looking at in portions of the video you can look at Title 9, Title 10, Title 11, Title 12, no babbling. Title 13, no babbling. Title 14, no babbling.

He does make during these times -- for instance in Title 12 he makes some nonspecific sounds, but again there is just no babbling. That just raises a concern to me that there is an underlying problem with language.

Q And did you see anything in the medical records that caused you to think that or that corroborated what you saw in the videos?

A Yes, I did.

Q And tell The Court what that was.

A Let's just first start by stating that in the regular pediatric care records in the first year of life there is a documentation, for instance, at six months and then 12 months, the physician does not have any concerns regarding development, but there is no documentation on specifics, and we'll take it at that.

But later on when we look at the evaluation, first of all, if we look at the evaluation by Dr. Otegbeye on June 11, 1998, he lists in there that the mother gives a history of a three-word vocabulary, mama, dada and sister's name.

Afterwards, the next documentation we have of language is in November 1998, on November 12, 1998, it says "spitting out a few words" but it doesn't say what they are. It doesn't say how they are being used.

In the referral to early intervention, they stated that he had a three to five word vocabulary. In the mother's handwritten record of her initial visit to Dr. Bradstreet that was in 1999, mother documents the use of five words, all names, mama, dada, and family member names, and nothing else, and basically states that there was just a speech arrest, there seemed to be a language arrest, again telling me that there seems to be this pattern of preexisting

problem of language, and it seems to me that the language stagnated sometime in the second year of life, and just didn't go anywhere, and this is what you can derive from viewing the video and looking at the medical records.

Q Doctor, have you seen patients that have presented with a similar picture, clinical picture as Colten Snyder?

A Yes, I have.

Q Based on your review of the records, when was functional improvement in Colten first documented?

A According to the available records, and this is early intervention, after he starts his speech therapy, the speech therapist documents as early as July 1999 that he is showing improvements in language. And if you go through her notes from that point on, she documents continuing improvement in language skills and play skills.

Q Doctor, does it surprise you that Colten improved with speech therapy?

A No, it does not.

Q Why not?

A First of all, for children with underlying language problems, whether or not they are related to autistic spectrum disorder or an individual by

himself, we know that intervention helps. We know that appropriate intervention helps, and obviously in this case it appears that he had appropriate intervention in terms of the speech therapy, and we know that we see growth. In other words, there's data telling us that this happens.

Q And do kids respond either better or worse to speech therapy based on their intelligence or intellectual capabilities?

A Well, I thought that the speech therapist gave a wonderful quote, and I'm going to again paraphrase her, that with the appropriate intervention children improve to their own intellectual and cognitive abilities, and that is basically the mantra that we try to push; that if you do the appropriate intervention children hopefully will get to the point that they were supposed to get to.

Obviously in Colten Snyder it was a very good point that he got to, and I'm glad that he did, so that it does not surprise me the gains that were present had occurred, did occur.

Q And just so I'm understanding you, are you saying that his great improvement is based in part on his excellent intellectual capabilities?

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A In part, it's based on what he has available to him; in other words, where his cognitive potential is. He clearly has a cognitive potential to be in the normal range, and he showed that, that that was there, and that's important because if cognitively you are destined to have an IQ of 50, you can do all the therapy that you wish and you're not going to get to an IQ of 125.

And while we look at the records, and in the records you can see that there is testing done initially which shows that he does not have good skills, this is the typical pattern of kids with ASD.

First of all, the cognitive testing that was done is limited because of levels of cooperation that were present so you can't get the best picture in the world.

Secondly, all that that testing tells us is where his language is at that point in time, where his function is at that point in time. It does not necessarily tell us where he is going to end up two, three, four years from now. It tells you where you need to start your intervention, and I think that his situation explains it very well because we see there is good growth in his developmental skills and his language skills from at least July 1999 onward.

Q And I believe you testified during the Cedillo hearing and presented a slide on something that you called the natural history of autism.

In your opinion, is Colten's improvement and course consistent with what you described as the natural history of autism?

A Yes, it's one of the developmental patterns that we can see, that you are worst at the second, beginning of the third year of life, and then you start showing improvement with the intervention, and you grow to your potential.

Q And, Doctor, do you treat any patients who you classify as having regressive autism?

A Yes, I do.

Q How many of your patients that have regressive autism improve to the point of being essentially normal?

A I don't have any who have done that.

MR. JOHNSON: I believe that's all I have. Thank you.

THE COURT: Mr. Powers?

MR. POWERS: Thank you, Special Master.

CROSS-EXAMINATION

BY MR. POWERS:

Q Good morning, Dr. Wiznitzer.

A Good morning, sir.

Q We have met before. Obviously we had a colloquy on your direct and my cross during the Cedillo case, and I do want to follow up on maybe a couple of issues that were addressed in Cedillo that were not covered today, but I will primarily focus on your expert report and the direct testimony that you have given here today.

I first want to talk a little bit about your expert report. Early on in the report you talk about some identifiable biologic underpinnings. Do you recall that portion of your report?

A Can you show it to me where it is?

Q Yes. Well, yes, it's on page 1. It's down at the bottom.

Q Which report, sir? I have two reports.

Q I'm sorry. It's the most recent one. I think it was described as a supplemental report. That's the one dated September 28, 2007.

A Yes, sir.

Q Okay. So now that we know the report we're talking about, the page we're talking about is page 1, and just down there at the bottom there is a discussion that you have about identifiable biologic underpinnings.

Now, you list marker chromosome 15 syndrome, Fragile X, tuberous sclerosis, and then certain in-born errors of metabolism. I was just curious what you were referring to by certain in-bred errors of metabolism.

A The classic one is untreated phenylketonuria, or PKU.

Q PKU.

A That's the classic. There is a representation that some children with mitochondrial disorders also will have an autistic spectrum disorder phenotype, so that's basically two groups.

Q Are there any others?

A There are some others, but whether it's directly linked to autism or whether it's just because of the severe impairment in cognition that's present that they also show autistic features is less well defined.

Q Again, the reason that it's less well defined is that there are other morbidities associated with the condition that are beyond what you would find in ASD?

A No. The more you have -- the more retarded you are the more likely you are to just show autistic features, even if you don't have autism. In other

words, if we look at a group of children with severe

mental retardation, at least 30 to 40 percent of them will show some behaviors that people would classify as beig within the autistic spectrum disorder.

Q Are there any other -- well, I should back up. Are these underpinnings, biologic underpinnings, are these genetically based, the ones that you list here?

A Yes.

Q So they are pretty much genetically determinative. If one has marker chromosome 15 syndrome, one would be autistic, would fall in the ASD --

A No. You may be autistic.

Q You may be autistic.

A Yes, there is more to it than just that. Thans just having marker chromosome 15.

Q Okay. But marker chromosome 15 is an entirely genetic issue?

A Yes, it is.

Q For the ones that you list here in this sentence about the disorders that begin with marker chromosome 15 syndrome, are there any environmental contributions that would be a biological underpinning to the presentation of ASD in children with any of those disorders?

A The only biologic underpinning in marker chromosome 15 is from which parent you inherit the chromosome.

Q And the same with Fragile X?

A No.

Q Is there any environmental contribution?

A In Fragile X, we don't know of any environmental contribution.

Q PKU, these other in-bred errors, metabolism, no environmental contribution?

A No.

Q How about tuberous sclerosis?

A Tuberous sclerosis, it's not truly an environmental contribution. It's really linked more to the early onset of seizures which is not environmental in itself. It's due to the underlying condition.

Q Yes. So the seizures are caused by the underlying condition, and the seizures then can create the conditions under which one might be autistic?

A Well, it's more complicated than that.

Q I was afraid it was.

A But there is an association.

Q Okay, thank you. That's fine.

Now, you also talk about the presence of

additional clinical features, certain in utero exposures. You describe Thalidomide, rubella or cytomegalovirus. Are there any other in utero exposures that you identify as a biological underpinning to ASD?

A I know there is a few more. I don't recall what they are off the top of my head.

Q Aside from what you've listed here in total in this paragraph, are there any other identifiable biological underpinnings?

A There is a gigantic list, sir. I just gave you examples.

Q And that's just what I wanted to get to. This is not necessarily exhaustive. This illustrative.

A Thank you. That's actually a very good description. Thank you.

Q I'm glad we're agreeing on some of this based on some of the things we didn't agree about in Cedillo, but I do just want to make clear that this is not intended to be exhaustive. It's illustrative.

A Yes, sir.

Q If you added up all the biological underpinnings, the ones you have listed, the multitude of ones that are out there, is there a way that you

can identify among all children with autism spectrum disorders what percentage of those autism spectrum disorders are caused by this entire constellation of identifiable biological underpinnings?

A The number that's proffered nowadays where you can do testing or there is testing available in order to identify it is probably as a minimal estimate 25 to 30 percent.

Q And that estimate of 25 to 30 percent, is that an estimate that you agree with?

A Yes. It depends obviously on the child. In other words, if I have a child who comes in with significant cognitive impairment, mental retardation is the relative term for that. If there were obvious more features, the number is much higher. Yet even in children who don't show those because of advances in technology we are finding more and more genetic underpinnings that are identifiable.

Q And that was actually a question I was going to ask. Has that percentage gone up over time?

A Yes, it has.

Q Okay.

A And it's expected to go up even more as some of the identifiable causes from the lab, if you want to say it that way, are transferred into the clinical

arena and the testing is made available to the general practitioner.

Q And so the identified biological underpinnings in 25 to 30 percent range, are those essentially genetic contributions to the appearance of autism spectrum disorders?

A Yes, and that does not account, for instance, the rare cases of cutomegalo virus, or I don't think we have seen congenitally developed, at least I haven't seen it in two decades.

Q Well, yes, and I wasn't trying --

A No, no, I --

Q -- about that.

A Outside of things like prenatal viral illness, we're talking about pure genetic.

Q Exactly.

A Yes, that would probably be a reasonable number. At this point in time the number will go up.

Q Do you expect that number to reach 100 percent?

A I don't think anything reaches 100 percent, and let me explain why. That even if we state with certainty that you know that something is a genetic underpinning, it does not mean that we have the technology available to prove the exact genetic

disorder, the exact genetic problem.

Q And when you say "underpinning," are you using that in the same sense as the word "cause"?

A Yes.

Q So when we're talking about the biological underpinnings to autism spectrum disorders, we're talking about identifiable biological causes?

A Yes, sir.

Q And at this point it's your testimony that we have identified -- we -- I say that as a lawyer -- as a doctor, I should be saying it as a doctor you all have identified that 25 to 30 percent of ASDs can be related to these identifiable causes, and aside from Thalidomide, rubella or cytomegalovirus, they are pretty much all genetic. Is that a fair statement?

A Yes. There is probably some in-utero exposures that makes contributions, but we know the ones such as Thalidomide. People talk about the contribution of things like valproate, especially in animal models, and perhaps some human data. There is other data suggesting some associations but no proven causation at the present time, but I expect that there very well may be some -- we'll say acquired in utero phenomena that would cause the autism. We just have to wait and see as we get better.

Q Do you believe that there are any postnatal environmental contributions to autism spectrum disorder?

A Not to cause what we would typically call autism, no. Not by itself, no.

Q What do you mean by "not by itself"?

A Well, there is data telling us that there are some epilepsies that present very early on, second year of life, third year of life, that will have autistic phenotype and that with intervention and with treatment of the epilepsy you can basically make the autistic phenotype disappear. In my own practice, I have a handful of children who have been successful with this kind of management.

I don't know that there is any proven certainty of any postnatal exposure by itself that will cause an autistic spectrum disorder.

Q Do you believe that there are postnatal environmental exposures that in the presence of a genetic anomaly might cause autism spectrum disorders?

A Well, let's not use the word anamoly

Q What word are you comfortable with?

A Well, I think when people talk about this, they say a genetic predisposition, or genetic difference, whatever terminology you want to use. Let

me answer it this way.

People have hypothesized this, it is a thought that has actually run through the community now. I am basically neither yes or no. I'm waiting for evidence to give me more information to confirm to me that this hypothesis really has legs.

Q And the hypothesis is that there may be genetic vulnerabilities or genetic --

A Good word.

Q -- predispositions that in the presence of a certain environmental exposure or -- yes, exposure -- can result in ASD?

A That is what people state. I have read a lot of articles, and all it turns out to be is personal opinions with no data, and it's a problem when people do this. I don't know if in science whether that is always the right thing to do. All you want to do is give your personal opinion and because of your name it carries some weight. I would like to see the data, and I think right now there is nothing to support that hypothesis, but I'm open-minded, and willing to consider all information, and I will change my opinion if information would sway me.

Q And that is actually -- you're getting a few questions ahead of me, but that was the question I was

going to ask, is obviously with IOM and NIEHS and academic institutions, et cetera, looking at this, I'll just describe in shorthand that the gene environment interaction is a cause of autism.

A People are looking at that, and that's why I say I am waiting for the information.

Q And you would be able to change your mind based on data that comes out that's reliable?

A Yes.

Q But again back to where we are today, would it be fair to say in your opinion between 70 to 75 percent of the cases of autism spectrum disorder, in your opinion, don't have an identifiable biological cause, is that correct?

A Let me back up and say I gave you the genetics.

Q Yes.

A I gave you the proven genetic testing and the proven let's say in utero exposure that we know about. In addition to that we also have families. For instance, let me give you some examples.

I have families where I have two or three children who have autism spectrum disorders. There is clearly a genetic predisposition that I haven't identified. I don't know what it is, and I can't

convince anyone in my medical center to do testing.

because it's such a small family unit the chances that you will find a gene is extremely doubtful. But the thing is we know that that's genetic, and there is a group of individuals, probably an additional 5 percent or so, some people quote a higher number, I'm being conservative, there is an additional 5 percent that you can add to the other number that I gave you before that clearly fall within that group, then in addition to that we've got the larger family unit of what's called the broader phenotype where there clearly are the relatives -- might be that there is an idiosyncratic cousin or uncle where you may not have full-blown features but enough that we call it the broader phenotype, and there is increased risk also shown further and children with autism that would not be surprising because there seems to be something running in that family that seems to be genetically-based, and that adds an additional number. You can't really say it's the 70 to 80 percent. You might have to narrow it down perhaps to more like 50 percent or so where we have no identifiable reason at the present time.

Q And then even in some of these family studies, I know that in Cedillo the issue of the twin studies was discussed. It was primarily by Dr.

Fombonne, I believe, addressed those studies. Even

given a high concordance rate of ASDs within sets of identical twins, in particular, that concordance rate didn't get to 90 percent, correct?

A Correct.

Q So that even where you have identical twins, there are presentations from the published literature where one twin has a autism spectrum disorder and the other identical twin does not.

A There is a very small number that's given, about 10 percent of that cohort, but from a science standpoint the idea that you have 90 percent concordance is very strong evidence that it's a genetic predisposition.

Q Certainly, and predisposition, and I appreciate we can continue to use the same terminology here because that number does change as one might expect for fraternal twins. The concordance rate drops and you have pairs where the number of ASDs and the number of non-ASDs, and you would expect that if you were looking at a genetic contribution, correct?

A Yes, sir.

Q And when I say expect that, the difference between the concordance rates between identical and nonidentical twins, you would expect that?

A Yes, sir.

Q But at this point there is no identifiable biological cause of autism, and we'll take the numbers that you now add up and try to keep track of somewhere in the range of 50 percent.

A Let's just use that number.

Q Okay, and I'm comfortable using that number. It sounds like you are. So in half the cases of autism spectrum disorder right now you're not able to say what the cause of the autism spectrum disorder is, is that a fair statement?

A If you're asking if I would give the specific reason outside of saying we have evidence telling us that it's most likely prenatally-based/genetic/some involvement with the chromosomes --

Q That is what I --

A -- genetic. No, I would state that the twin studies tell us that the vast majority of those kids probably have something wrong with the chromosomes, in other words, with the genome that they have not yet identified.

But if you're asking me have we identified the reason, the answer is no. That's a better way of answering the question.

Q Now, any of these biological causes that we've discussed required -- I know this has turned

into a fairly long list taking off what you had in your report -- are any of these biological causes or any other biological causes known to be associated in particular with regressive autism?

A The tuberous sclerosis kids are, the epilepsy children are, the mitochondrial disorders are.

Q Any others? And I don't want to cut you off. It looks like you're still considering it that question.

A There are others. I can't give you them off the top of my head.

Q And collectively with those known biological causes related to regressive autism, do you have an idea of what percentage of regressive autism cases could be tied to one of these known biological causes?

A We don't have numbers, no.

Q Have people looked at that issue?

A They've looked, but the problem is that it's a biased sample. It's not like you're looking at population. There are papers out there saying there are a large number of them that are mitochondrial, but if you look you will find a mitochondrial disorder that's present. But again it's a biased sample because they may have been referred to a center

because they specialize in mitochondrial disorders.

I don't know of any good population surveys that actually addressed your question.

Q And just to be cautious then, would it be fair to say that based on the lack of data you cannot answer the question of what percentage of repressive cases are caused by these known biological agents?

A Yes, and one more thing because we need to add there, is also how people define regressive autism, whether they are using the stricter I think, -- I think we had a discussion about this last time

Q We had a long discussion about this last time.

A Whether they are using the stricter criteria of totally normal development with a clear, defined loss of things like functional language and things of that nature or whether they are basing it on someone coming in and just reporting it without checking the specifics of it. And there are papers out there that actually state, we didn't check it. Were listing it but that's what were told it was. That data has to be taken for what it's worth.

Q Now, you also in your report, and I'm just flipping to page 2 of the same report, moving onto a different issue here, at the very beginning the statement is that between one-forth and one-third of

the children with ASD had a history of autistic regression is elicited. Is that a history that's elicited by a treating physician?

I'm just trying to figure out where that number -- is that your --

A No, that is what people have written, my experience is more like 15 to 20 percent. This is what people write in the literature, and I think you

noticed that the history is elicited but the last sentence of that paragraph says, "In retrospect of evaluation, clinicians frequently identified developmental abnormalities occurring before the Frank appearance of apparent regression.

Q Right, and that's why I was asking you about the history being elicited because I contrasted that sentence --.

A But it's just the history of someone saying there was an obvious regression.

Q In the case of Colten Snyder, you described some evidence that you identified as signs of developmental delay, and when I was listening to your testimony and taking what notes I could, it sounded as if it was all related to language use, is that correct?

A Yes, that's really all I had a good sample of on the video tape, and therefore that's all I could really comment on, and that's the information that's most apparent in the contemporaneous medical records about language.

Q And now, if I recall, there are three different domains that one tests in diagnosing autism spectrum disorder. Language is one of those, correct?

A Yes. Communication is a better word.

Q Well, I do want to use your language. What are the three domains that you identify as the

diagnostic criteria for autism spectrum disorder.

A Significant qualitative impairment of socialization, significant qualitative impairment of communication and restricted interest/repetitive behaviors.

Q Now, in your review of the videos and the medical records, you've already identified what you believe were some communication or language developmental delays, is that correct?

A There were clearly problems with language.

Q Yes, and in the social domain, there is nothing in the medical record and nothing in the video that would indicate a deficit or delay in social skills?

A There's not enough to answer that question, there is some soft information about some subtle differences in social behavior, but nothing concrete, nothing severe, will just say they've subtle, and if I may, I will even identify titles and you can go back and look at the video.

Q Well, actually hold that thought for just a second because I have some follow ups, but I am going to ask you to --

A Well, let me answer your third one. The third one is there is -- the restricted

interest/repetitive behavior.

Q No, I haven't asked that. That was your domain but not yet my question.

A Okay, sir.

Q In the social domain, you're going to give us some references that you see as subtle, but my question was there is nothing in the medical record, there is nothing in the parents' testimony or caregiver's testimony to give rise to social deficits in Colten before the age of 15 months?

A There is nothing in the medical records one way or the other, and the testimony that was given by the parents, by the mother, by his mother and his aunt did not have that information, I agree.

Q And in fact the testimony of his aunt and his mother indicated that in fact he was very socially interactive, have social skills, play skills with other children, relational affinity towards relatives and friends. You remember all that testimony, is that correct?

A Yes, sir.

Q Now if you could just go ahead and just list the areas where you see that there might be some subtle issue with social issues.

A Let us start with Title 7 which is when he was 11 months old, and about one minute into the

video. He is called many times, doesn't respond much to being called.

Q And how long does that sequence last?

A According to my notes, probably less than 30 seconds.

Q Okay. Other slides?

A Title 8, I have a note but I don't say when it is, but when his name is called, he doesn't turn.

Q How old would he be at that point?

A Thirteen months old, and at 13 months old on Title 9 it's written that there is not much of a response to a hug. On Title 10, does not specifically look, had to be prompted to do certain relative to looking behaviors. Now in that he goes to his father, to give credit. There are no sounds that are made.

On Title 11, nonresponsive --

Q I'm sorry. But I was unclear what the issue was there. You said he's going to his father so he is being social but there is a communication --

A No. There is evidence of differences in social behavior but there is also evidence of social behavior.

Q Okay.

A I'm just giving credit where credit is due.

On Title 11, there is no response to voice.

On Title 13, he ignores his siblings, and that's all I think we have that I have of a sample. That, to me, is all subtle, and I'm just pointing out that it's there, and I'm not saying anything more than just that those behaviors are there.

Q And it would be fairly common, wouldn't it, for a completely normal 13-month-old to occasionally ignore his parents when they call his name, isn't that correct?

A I agree, but if it was just once or twice that I saw it on there, I wouldn't give it any credence, but the thing that I saw patterns of behavior

Q And these patterns are a couple of seconds at a time, 30 seconds at a time?

A Some of them, yes.

Q You've already described the language, or excuse me, communication, communication issues. Let's talk about the repetitive behavior. Anything in the medical record to indicate stereotypical behavior or repetitive behavior that would be associated with ASD?

A I'm assuming you're saying -- at what time, time period?

Q Before his MMR.

A Okay, sir. Let me just say there are

comments after, you know, in terms of Dr. Bradstreet's

notes, but there is not really any explanation of what they are. There is no documentation of the specifics. It just says has some self-stim behaviors, but nothing more.

Q But you did hear testimony about repetitive play behavior from the family.

A But that's play behavior. That's not -- that's play behavior. That doesn't have any bearing to repetitive behavior. That was there. But there is nothing before that I could basically pin my hat on.

Q So those are the three domains, and we are going to move on a little bit to talk about some other issues that came up in your direct.

For the language issues that you describe, the communication issues, particularly by the age of 13 months, I think you used a decrease in expected languag use at the age of 13 months.

A There was no language use. There were no words. There were some syllables that you could count on one hand the number of times that you document despite interactions with multiple individuals, interaction by multiple individuals in the environment. So there was just no -- nothing.

Q And that's based on your review of the videos?

A Yes, sir.

Q You were here for the testimony of Colten's family members?

A Yes.

Q And I assume you heard that the parent report of word use by 15 months was between 15 and 20 words. Do you recall that testimony?

A Yes, sir.

Q Word use of vocabulary between 15 and 20 words by the age of 13 months.

A Fifteen months.

Q Fifteen months, yes, we're talking about your view of the video is 13 months.

A Yes, sir.

Q By 15 months, 15 to 20 words, is that in the range of appropriate vocalization?

A If the words are used for functional purposes, the answer is yes.

Q And as you sit here today, you don't know one way or the other whether they were used functionally as you would just describe it?

A Assume that that history is accurate, yeah, I don't know.

Q And so what you then see is the use of two to three words at 13 months.

A Excuse me?

Q So you see the use of two to three words at age 13 months?

A I saw no words. I heard some syllables, a ba, a ma, and a baha. If you play back the video and watch it, and you're welcome to do so, sir, you will notice that there is no real syllabic babbling or polysyllabic or multisyllabic babbling such as I would expect in a child of that age.

Q So a child at the age of 13 months then, two months later is being described as having between 15 and 20 words.

A It's interesting, the description is the description we heard in the courtroom in 2007, the description is not what's documented in the medical records of 1998.

Q You then went on to talk about the lack of words, at this point two to three words and language arrest that were noted in the reports of Dr. Otegbeye and his developmental referral, and then by Dr. Bradstreet's initial intake.

A Dr. Otegbeye did not state anything about language arrest. Dr. Otegbeye just basically documented a three-word vocabulary, and this would have been at age 17 months.

Q And this would have been after the

administration of the MMR?

A Yes, sir. And more important, Dr. Otegbeye did not document any history that was given of a loss of language.

Q And the fact that he didn't write it down, the lack of any note of his is not dispositive as to whether it had actually occurred or not.

A Well, I would agree that one note would be telling, but when you look at the note from the week before on the nursing admission to the hospital when he was admitted on May 26th, there is no documentation in the nursing admission of any loss of language either.

Q And he was going to Dr. Otegbeye for the possibility of juvenile rheumatoid arthritis. Is that one of the bases for the referral?

A Yes, sir.

Q So it's conceivable that on intake they were not asking questions related to the entire history of this child's communication and language histories?

A I was impressed that he actually took a history of development, and I think at that time it would be an opportunity that if there was a concern about the loss of skills, it would have been articulated.

Q But again, the fact that it's not in there

you can't say here right now one way or the other whether it happened or not?

A The fact that it's not in there basically just says it's not in there. That's all.

Q Okay. And then with the referral to early intervention, there is the other referral to language, the lack of language, language delay, that also was post-MMR correct?

A Yes, sir.

Q And very obviously Dr. Bradstreet's records and the mom's notes that are contained in those records, that will all be after the MMR.

A Yes, but let me just say one thing, sir. Yes, it was after the MMR.

Q Now, you talked about briefly the speech therapy that he had with a professional language therapist, and we've heard her testify. Your testimony was that he showed an improvement in the language during the course of and by the conclusion of his speech therapy. Is that a fair statement of what your testimony was?

A Yes, sir.

Q Now, this improvement -- in the course of this improvement also saw the implementation of a special diet, the GFCF diet, gluten-free casein-free

diet, that's correct, isn't it?

A Yes, sir.

Q That interval in which his language improved posttreatment included the IVIG administration by Dr. Bradstreet, correct?

A Let me make sure I have your question correct. You're saying that during the time period that we were already seeing the improvement in the language, during that time period, that was the time period from July of 1999 onward when the speech therapy was actually stopped, during that time period IVIG was started in March of 2000, the answer is yes.

A And there was a course of IVIG treatment that was given simultaneous with a significant period of his speech therapy, correct?

Q There was a course of -- yes, yes, with a significant time period during which he was undergoing speech therapy, yes, sir.

Q There was also a program of nutritional supplements that Dr. Bradstreet was recommending to the family that Colten was using, that was ongoing during the time he was undergoing speech therapy and showing an improvement, correct?

A Yes.

Q And the improvement also followed after the

administration of Secretin by Dr. Bradstreet?

A The improvement was temporally associated with the giving of Secretin, yes, it was.

Q And I should make clear, were you here for the testimony of the speech therapist?

A Yes.

Q Okay. You also recall that the speech therapist reported that Colten's progress was very unusual and quite striking. Do you recall that?

A I don't remember those exact words. But if you represent them to me that way, I will believe that.

Q And I'll be careful, I won't say those were necessarily her exact words, but do you recall that the tone of her testimony was that Colten made unusual and fairly dramatic progress during the time that she was taking care of him? Excuse me. Not taking care of him, but working with him.

A May I change the wording? That she was impressed by the amount of improvement that he made. Is that a better way of saying it?

Q It says the same thing, but I'm fine with that.

A And especially when she represented to us with a small number of individuals with autism to whom

she was actually providing services at that time, it would not surprise me that she would make that kind of a statement.

Q In your expert report, sort of jumping back and forth, but I'll try to track this as closely as I can, on page 2 further down there is a paragraph right above the section that's entitled "Measles as a Cause," et cetera.

A This is again the 2007?

Q Yes, just so you know, Doctor, if it makes it easier to move among the documents you've got on the stand, the only report I'll be referring to is the 2007.

A Thank you, sir. Yes.

THE COURT: So that's Respondent's Exhibit Y?

MR. POWERS: Yes. Thank you, Special Master, and it's page 2 of Respondent's Exhibit Y that I will refer to.

BY MR. POWERS:

Q In that paragraph, it lists a number of treatments that you've identified that Dr. Bradstreet administered to Colten Snyder. Do you see the paragraph that I'm referring to?

A One more time tell me which paragraph.

Q It is one, two, three, full paragraph number four

A Oh, I see. Right above measles.

Q Yes, right above.

A I misunderstood you. I thought you meant right below measles. Yes, I see it, sir.

Q Okay. Now, you list the treatments and then describe that they have not been shown to successfully treat the central nervous system manifestation of measles virus persistence on and on. I'm not going to read the whole thing. I get in trouble with the Special Master if I start reading entire sections of a report. But I want to focus on that issue for just a moment. I want to ask a question that rephrases that a little bit.

Have any of these treatments been shown to successfully improve the symptoms of children with autism spectrum disorder?

A Which symptoms?

Q A: Are you talking I'll keep it broad and let you talk about the core symptoms or just the behavior.

Q What distinction is there between core and behavior symptoms then?

A I'm glad you asked that. I will now answer

your question, and it's part of your answer seriously.

It's part of your answer, and let me say it this way by proffering the concept which is not unique and given; that children with autism spectrum disorder are allowed to have other problems. I think everyone would agree. They are allowed to get colds not, it's caused by the autism. They are allowed to have allergies that are not caused by the autism. They are allowed to have food intolerances that are not related to autism, and we can keep going on and on. They are allowed to break their arm and it's not necessarily due to the autism, and I think we had that situation in this case also later on.

Getting put on the gluten and casein-free diet and reporting that there are improvements in behavior does not mean that there is a cause/effect relationship between the gluten and casein-free diet and the autism. In my hundreds of patients in my practice who have been on the diet, the only parents who reported improvements are those in whom the children appear to have a problem with milk or a problem with gluten product, and it would not surprise me, one in 250 to one in 500 children are gluten intolerant. They have celiac disease.

There is a much larger percentage -- in fact, I will wager that if I go through this room I

will find a few people who are lactose intolerant. I'll find a few people here who had milk allergy when they were younger, and Colten Snyder clearly had problems with milk that's well documented in the medical records -- what struck me the medical record was that mom stopped this at 18 months, gets put back on milk, he deteriorates. Take him off the milk, you see improvements in the behavior, better responses to speech therapy and such.

It is not saying that the gluten and casein diet is treating the autism. The gluten, a more practical interpretation there is that gluten and casein-free diet is treating a food intolerance/allergy that was preexisting and was aggravating his behavior and making him miserable, but he wasn't able to articulate what was going on with him. I have seen this over and over and over again.

Now to get more specifically to your question, there is clear-cut data that Secretin doesn't work. There are NIH-funded studies, the NIH spends over a million dollars funding several studies, double-blind placebo controlled studies that show that Secretin had no impact on autism. There are other articles in the literature that Secretin had no impact on autism. Unpublished work we did in our medical

center would basically be dated and then ask for documentation from individuals who didn't know that the children had gotten treatment, who were unable to verify the significant improvement in autism that has been claimed with Secretin.

But I think the most telling information for Secretin was that the parent of one of the children, one of the children that Dr. Horvath originally reported, actually got the patent to Secretin, formed a company called Repligen, did Phase 3 studies. This is what the FDA mandates you are going to do before you bring a treatment on the market, a medical treatment on the market, and these Phase 3 studies failed to show any improvement in the autism in the population, and I haven't heard a peep from that area since then... --

Q Certainly in that study it wasn't that every single subject in the study showed no improvement.

A Oh, no.

Q So I just want to make clear what you're saying. You're saying that in the studies that have dealt with Secretin, those studies have not found that what is -- I mean, because some of these studies some of the kids did show improvements.

A But the question there is, sir, again going

back to why did they show improvement. They may have

some underlying problem. There is two possible reasons. One is it could be a placebo effect. If you look at the Levy's work in Philadelphia, she actually documented the placebo effect that Secretin engendered in the population because she went back and interviewed parents about this later on.

We also saw a placebo effect in the work that we did. Parents want to see improvement, or the child was showing improvements from the natural history of the disorder -- we're talking about the autism -- that were proscribed a treatment that was done temporally at the same time.

Now, I'm not talking at all about Secretin doing something for your bowel, or if you have some diarrhea illness and Secretin. I'm talking about treating actually the autism itself.

Q Which then brings me back to this definition of core symptoms. So the core symptoms of autism would be those symptoms that give rise to a diagnostic conclusion across one of those three domains?

A Yes, sir.

Q So it would be your testimony that none of the treatments that are elicited here that you describe have any effect on the core symptoms?

A None, and if I also may state, for chelation

therapy there is no data one way or the other to state whether it does or doesn't do anything, and number two, there is not good biologic model to support that the issue of heavy metal, "poisoning" or elerated heavy metals in the blood have a causal relationship to autism.

When it comes to the issue of IVIG, there is no good data to support its use. There is just no good data. The studies that have been done have significant flaws within them from a study design standpoint that is very difficult to take that information and extrapolate it, and say see, it does have an effect on the core features of autism, which is why this canadlan group that Dr. Zweiman mentioned earlier basically came to the conclusion that they made the recommendation that it seems to have no effect.

The American Academy of Pediatrics basically has stated that there is no data to state whether it does or doesn't work because the work that's been done, the research work that's been published is inadequate to support the conclusion that it does work.

Q So in some of these cases there is research data that's been published and you're saying that you

don't think that it establishes efficacy.

A I'm not the only one who says it.

Q I understand. I understand.

A There are large groups of people who say that.

Q I understand.

A I'm just basically quoting what those individuals say, and again it gets down to the bottom line. When you do these kinds of treatments, and I think a very telling example of this is the issue of nutritional supplements. There was a case report in the New England Journal of Medicine.

Q And is this a report that's in the record?

A No, no, no. I'm just saying this as an anecdote unless you don't want me to say it.

Q Yes. Let's stick to the questions that I'm asking. I mean, you sort of had the opportunity to wind up and go forth on direct. I just want to focus on some questions that I want to ask you that are specific.

A Okay.

Q On page 3 of your expert report, I'm sorry, Respondent's Exhibit Y, if you look at the paragraphs starting at No. 2, early in that paragraph you say that Colten Snyder did not show any evidence of inflammation, including any neuroimaging.

Do you see the line that I'm talking about?

A Yes.

Q Now, Colten Snyder did have an MRI done in 2006. Do you recall seeing that in the medical records?

A Yes, sir.

Q And there is nothing in the medical records of any neuroimaging that was done on Colten Snyder before then, correct?

A Correct.

Q So the fact that there is no evidence of inflammation on neuroimaging, there is no imaging to rely on. So whether there was evidence there or not, we just don't know because there is no imaging done.

A Contemporaneous. You're saying at what time? 1999?

Q I'm say anytime before January 2006.

A There is no imaging, that's right.

Q Skipping pretty much further ahead in your report on page 4, there is a partial paragraph at the top of the page. It talks about prenatal viral exposure as a potential cause of ASD, but there is poor support for postnatal causation. I just wanted to make clear that in that sense you're talking about specifically postnatal causation on viral exposure?

A Yes.

Q It's not a more general statement about other postnatal exposure?

A Right.

Q Okay.

MR. POWERS: Excuse me. Special Master?

THE COURT: Yes.

MR. POWERS: I still have a fair number of questions to go, and I don't know if we necessarily need to take a lunch break right now, but can we perhaps take a 10-minute break.

THE COURT: If we're going to take a break why don't we take the lunch break. It's now afternoon. If that doesn't interfere with --

MR. POWERS: I have at least probably a good 30 minutes.

THE COURT: We're on point to have three witnesses today. Do you anticipate that we're going to have problems getting your third witness in if we recess from now until about 10 after one?

MR. JOHNSON: I will answer that question no, but it's conditioned upon the fact that Mr. Matanoski is going to be doing the questioning, and he's not here, but I believe that that should not be a problem.

THE COURT: Okay. Why don't we do the lunch break now rather than take another rest break.

MR. POWERS: I appreciate that, Special Master.

THE COURT: Okay.

MR. POWERS: So you're saying 1:10?

THE COURT: One-ten.

(Whereupon, at 12:10 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 1:10 p.m. this same day, Wednesday, November 7, 2007.)

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A F T E R N O O N S E S S I O N

(1:15 p.m.)

THE COURT: We are back on the record in the Snyder case, and you may resume your cross-examination.

MR. POWERS: Thank you, Special Master.

Whereupon,

MAX WIZNITZER

having been previously duly sworn, was recalled as a witness and was examined and testified further as follows:

CROSS-EXAMINATION (Resumes)

BY MR. POWERS:

Q Welcome back, Dr. Wiznitzer. We spent a good chunk of the morning, obviously, asking a number of questions. I'm going to pick up with some more questions.

At the outset though I did want to go back to an issue that you had talked about before and that was the issue of language delays and communication delays that you believe were present in Colten Snyder before he received the MMR. Do you recall that line of questioning and discussion?

A Yes, sir.

Q Do you recall a medical record that was

created by Dr. Sahai where he actually received the MMR, and this is Petitioners' Exhibit 8,115.

A 8?

Q Yes. It's page 115. I think there are a lot of pages in that exhibit, but it's page 115.

A Give me a second. Okay, what page, 115?

Q Right.

A I have it.

Q Okay. And under "objective" you do see that Dr. Sahai noted that there were no signs of any receptive language disorders, correct?

A Yes, sir.

Q So that is a medical chart note reflecting at some point in Colten's development the lack of disorders and at least part of the domain of communications, correct?

A That is in the office because that is the objective portion. In the office, that was the observation of Dr. Sahai, yes, exactly.

Q And then I hadn't thought to ask this before, but up above there the head circumference is the 45th percentile. I know that there were discussions in the Cedillo case about head circumference and accelerated head circumference growth.

I didn't see anything like that in your report in this case. It just reminded me to ask. You don't see any dysmorphologies with Colten Snyder based on a review of his records suggestive of an association with ASD? I saw nothing in your report indicating that.

A I wrote nothing about that, but children dysmorphology is not that certain. Dysmorphology is appearance.

Q Yes. I should have mentioned that in two separate questions. There is nothing about the head circumference to suggest the rapid growth of the head?

A There is no information available telling us that there was any kind of acceleration in this case.

Q Okay. And since I didn't see that in the report, we wanted to confirm that that's not part of your assessment of this case, and I saw in the report that there were no notes of any dysmorphology. So you haven't noticed any dysmorphology that would be a basis of your opinions?

A I found no comment about that.

Q I want to now talk again related to this language issue. In your clinical practice, and this is something we talked about in Cedillo so I don't want to go through it at length, but if you recall, we

discussed a procedure that you use to examine and diagnose children in your practice. Do you remember that discussion?

A Yes, sir.

Q Specifically, I would just like to ask you, focusing on your diagnostic method in your practice for giving an exam to children, what sort of tests do you do to make a decision about communication skills and language development?

A Test scoring or just inquiries and assessments?

Q I was using the tests, there were test variable, inquiries and assessments, questionnaires, whatever it might be.

A I take languages -- and I think you made a good observation here that on April 23, 1998, there is no sign of any receptive language disorders. Mine would actually be documentation in the subjectively historical portion -- what the child's language function is in terms of how many words this child is using, what kind of words they are, and what the use is, that's number one.

Number two is questions about comprehension, level of comprehension, sophistication of comprehension and used specifically based on ages.

Number three is other associated or pragmatic skills such as waving, clapping, pointing if you're at the appropriate age, things of that nature.

Q And if I could, so those would be things that wouldn't necessarily be words, but there would be other key indications skills that would be age appropriate?

A And that's why I use the word "communication" versus "language", because communication is more than the spoken word.

Q Right.

A Obviously, with that we also mean things like eye contact, facial expression, body language, things of this nature.

In the office setting, I also make observations, what the child does, how the child responds, is the child showing attention and interactive abilities.

Then if I have concerns, I basically set up a more formal evaluation. I usually refer them to our early -- because we're talking about preschooler, I refer them to the early intervention team simply because it's a free assessment and they give me the information that I want. If they are a little bit older, I get them assessed in the school system. If

there are more issues, I get them sent to one of our speech and language people or to one of our psychologists.

Q And in this case obviously with Colten Snyder none of that happened. You don't do any of that type of workup of Colten Snyder for the obvious reason that you weren't seeing him as a patient, correct?

A You're talking about at that time, in 1998? I did not do that in 1998.

Q And your review of his case and your assessment of his development is based entirely on the video that you saw, the medical records that you reviewed in their entirety. Anything else that you're basing that on?

A No, I'm basing it -- and the testimony that I heard in the court.

Q That would include Dr. Bradstreet, Colten's mother, Colten's caregiver and the speech therapist?

A And specifically when you mention Dr. Bradstreet because I know that he stated during his testimony how specific he is about making sure he gets good and accurate environmental information, and that's what I was pointing out in the mother's questionnaire that the mother filled out in the

office. There are no comments and quotes on the side in the margin that Dr. Bradstreet -- that he's questioning the language history that she provided to them.

Q Actually, I was just looking to make sure that we understand exactly what you're relying on to provide your opinion, and it sounds like we pretty comprehensively covered that.

A Yes, sir.

Q Okay. I now want to turn to this issue that you discuss at some length in your report, your critique so to speak of Dr. Kinsbourne's mechanism, the excitatory and inhibitory model that Dr. Kinsbourne describes at length in his report.

I see your summary of it and you obviously disagree with the conclusion, but I want to go to Dr. Kinsbourne's report, and find out from you what elements of that report, specifically what mechanism that you specifically agree with or disagree with. So it might help here if you have -- do you have Dr. Kinsbourne's report?

A I'm pulling it out as we speak.

Q Let me know when you have that out and I will try to --

THE COURT: And you're referring to

Petitioners' Exhibit 29.

THE WITNESS: Yes, ma'am. That is the one dated August 24, 2007.

THE COURT: Okay. Petitioners' Exhibit 29, and then if you can just let us know what page you're on.

THE WITNESS: Yes, Exhibit 29.

BY MR. POWERS:

Q Exhibit 29, and these would be pages 18 and 19.

A In his report?

Q In his report.

A Okay. Let me then get to that, sir.

MR. POWERS: And as you turn to that, Special Master, I want to make it clear here. There will be times I'm reading from this and it's not an attempt to read it from the record but rather than trying to --

THE COURT: Paraphrase.

MR. POWERS: -- paraphrase it --

THE COURT: This is a perfectly appropriate time to read.

MR. POWERS: I'm just nervous about that based on --

(Laughter.)

THE COURT: I'm sorry, I had Dr. Oldstone read to me a lot, and I could have recited it from memory at one point. If it's on the screen and we're all able to see it, that's one thing. But if you are orienting a witness to specific language, that's another.

BY MR. POWERS:

Q All right, Dr. Wiznitzer, are you on page 18?

A Yes, sir.

Q Okay. If you go to the very, very bottom of the page there is a fragment of a paragraph, and the first word in that paragraph is "Glutamate".

So what I want to ask you is do you agree with the statement that Glutamate is the predominant excitatory neurotransmitter in the brain and the chief inhibitory neurotransmitter is GABA?

A Yes.

Q Dr. Kinsbourne then goes on to say that the balance of the levels between these two neurotransmitters is a main factor determining the level of excitation/inhibition balance in the brain.

Would you agree with that statement?

A Yes.

Q He then goes on to say that the excess

glutamate is harmful, the levels are normally tightly controlled in the synapse.

Is that accurate?

A Yes.

Q He then goes on to say further that excessive glutamate flow, on the other hand, depressed GABA flow can lead to an overexcitation and at the local level cytotoxic that can cause brain cells, including neurons, to die.

Is that an accurate statement?

A No.

Q What about that statement do you believe is inaccurate?

A Depressed GABA flow is not really what leads to cell death. It's excessive excitation of glutamine.

Q So would it be your belief that GABA flow -- let's say that glutamate flow remained the same and GABA flow went down. Would that lead to overexcitation?

A No. Not overexcitation of the type that would be cytotoxic.

Q Okay. But would you agree with the part of the statement that says "excessive glutamate flow would lead to overexcitation --

A I don't know what flow means, but we'll say excessive glutamate in the postadaptive region. In other words, too much glutamate that is overexciting the cell, the neuron is specifically what we're talking about here, will cause cell death, yes.

Q He then goes on to say that pyramidal cells are particular vulnerable targets for cytotoxic damage due to glutamate.

Would you agree with that?

A I don't know of any data telling me that pyramidal cells are more or less vulnerable than any other neuron.

Q Aside from the presence of any data that you may or may not know about, does that sound like a reasonable statement to make medically?

A No, I would just say that the vulnerable targets, and any neuron exposed to excessive amounts of glutamate, in fact, especially when they have the problem with glutamate receptors, can have a sudden toxic death, yes.

Q He then goes on to say that the depletion in the number for purkinje cells in the cerebellum and frontal cortex that has been demonstrated in the brain of individuals with autism may represent the cytotoxic effect.

Do you agree with that statement?

A No.

Q What about that statement do you disagree with?

A I think there is no data to support his conclusion that it represents a cytotoxic effect.

Q Do you disagree --

A If I can just finish. The purkinje cells basically hang on the cerebellum. The frontal cortex is not a typical neighborhood for it.

Q Do you agree with that portion of the statement that says, "depletion in the number of purkinje cells in the cerebellum and frontal cortex have been demonstrated in the brains of autism"?

A No. A decrease in the number of purkinje cells in the cerebellum hasn't been demonstrated in the brains of individuals of autism, yes.

Q So you would agree with that part but you do not think it represents the cytotoxin?

A I think that that is conjecture and speculation.

Q Is there any evidence that you're aware of that would argue that it does not represent a cytotoxic effect?

A There is no evidence one way or the other.

Q Okay.

A The evidence that we have about this kind of cytotoxic effect is that there is no evidence of scarring in the region, suggesting that more likely than not, the phenomenon may occur prior to birth before the scarring system is in place in the brain.

Q And the work that you're describing on there, have you filed that in Cedillo or in this matter?

A It's listed in et al. Any pathology that's written about this, this is common knowledge to anyone who works with autism. Of course, I'm blanking on the man's name from UCLA who wrote a paper that actually describes the absence of cerebellum purkinje cells in the autopsies of individuals with autism.

Q And the reason that you don't think it represents the cytotoxic effect is the lack of scarring, is that correct?

A No, there is no scarring, and number two, we just don't know whether or not they are there. It's a presumption that it's due to cytotoxicity.

Q Dr. Kinsbourne continues that the same may apply to the loss of synaptic connections and diminished dendritic growth in the hippocampus in autism. Do you agree with that statement?

A No.

Q What about that statement don't you agree with?

A Well, if you get enough cytotoxic effect, you're going to kill the cell. It's not going to change the number of synaptic connections. It's not going to decrease the amount of dendritic growth. You're going to kill the cell.

Q And that actually then leads into the next statement I want you to take a look at where Dr. Kinsbourne says that "Assuming a lower level of imbalance, few, if any, cells may actually die, but overexcitation will have predictable effects on the functioning of the brain." Do you agree or disagree with that statement?

A I disagree only because I think that it's speculative with no data to support it.

Q Are you aware of any data that would address that issue that contradicts it?

A Let me just say it this way. In science, it's not that I have to contradict someone else's hypothesis or speculation. They need to prove it to me.

Q I understand that, but all I'm asking is are you aware of any studies that have looked at this

issue and reached a negative conclusion?

A No. As far as I have looked at this issue, let me explain that the idea that somehow you can and a, balance is conjecture; that there is going to be excessive glutamate in the synaptic cleft just enough to overexcite the cell but not enough to kill it doesn't make sense.

If you really have a fine-tuned mechanism, which is what he says has been lost, that control mechanism that has been lost, you're going to get too much glutamate building up, and there is going to be cell death period. It's not going to stay at a certain level. It's going to get worse and worse and worse because there are no cleanup components there, because he stated that it's missing.

And we know that the glutamate transporters that are in the neurons are insufficient to pick up the slack because the predominant glutamate recovery system that is in the brain is in the astrocyte, not in the neuron. That's the one that keeps the area safe. His statement that the astrocytes are no longer doing what they are doing would mean that sooner or later poison is going to build up, it's going to kill the cell.

Q And we'll get to the astrocytes in a moment,

but with this particular point then, you just don't think that cells would survive this overexcitation process?

A Well, my impression here is that the chronic overexcitation, you're not talking about an acute stressor. If you just have an acute stressor, the answer is yes, cells do survive.

Q Okay.

A An acute stressor. But his explanation that I heard was not that of an acute stressor but of a chronic process. Please correct me if I'm wrong.

Q I'm taking the answers based on your understanding.

Now we move on to talk about "The obvious effect is to render the brain more apt to generate epileptic discharges." Do you agree with that statement?

A Yes. Excessive glutamate will do that.

Q And you would also agree the epilepsy as well as subclinical disturbances of the EEG are common in autism spectrum disorders?

A Yes, but there is a caveat, and it's important to bring the caveat in that he's representing to the Court that this is due to some glutamate imbalance. If this was due to glutamate

imbalance where we do have some unfortunate, what's the word, experiment of nature that occurred in children where this happens, it doesn't take years for the seizures to happen. They happen right away.

And in autism, the onset of seizures is not at age one year, it's not at age two years, it's not at age three years. In the classic, we'll call it the primary autism population that we're talking about, the onset is at adolescence and young adulthood. That is far too long a time period for this overexcitation to occur and no seizures to be present.

Secondly and another important point in that matter is that you have to ask yourself a question who are the individuals that are most susceptible to seizures. In other words, if I look at the entire ASD population, who are the individuals who are most likely to develop seizures in adolescence and young adulthood, and the individuals who are most apt to do so are the ones with mental retardation.

In other words, the lower the IQ, the more likely you are to have seizures, suggesting it's not a glutamate phenomenon at all, but it's a wiring issue that's directly related to the intellectual impairment associated with mental retardation.

If we look at those individuals with normal

intelligence, their risk of seizures while slightly above the general population is not that high. Therefore, there is a good alternate explanation. Actually not even an alternate. There are good explanations why seizures occur, that we don't have to posit a speculative hypothetical model such as Dr. Kinsbourne has provided.

Q But given the caveat, you would agree that epilepsy and subclinical disturbances are present in ASD children?

A But the subclinical disturbances, and Dr. Kinsbourne comments on subclinical disturbances, the majority of the subclinical disturbances on the EEG are not epileptical discharges. It's really back on -- which has nothing to do with glutamate. In fact, if you are going to argue that it's because that part of the brain is underexcited and that's why it's behaving in that manner, it's only on older individuals who have the epileptical discharges.

Q Now moving along, you started talking about the astrocytes, and we're going to discuss it right here. Obviously Dr. Kinsbourne does. He says that "One of the functions of astrocytes is the regulation of levels of glutamate at the synapse." Would you agree with that statement?

A Yes.

Q Also that glutamate transporters are expressed on the astrocytes. Is that something you agree with?

A Yes.

Q And further the astrocytes form a sheath around the glutamatergic synapse, and the glutamate transporter intercepts and mops up spare glutamate.

A Well, I wouldn't normally use the word "mop up".

Q I knew that you wouldn't, but do you agree with just the statement?

A Let's use the word "recycle". The body is the original glutamate recycler. It recycles because it does not like to waste it.

Q So if we substitute the word "recycle" for "mop up", you would agree otherwise with that statement?

A Yes.

Q And that by doing so, it prevents it from spreading to other synapses, that is, the glutamate spreading to synapses?

A Yes.

Q And this is a way that the astrocyte --

A Let me say it's not only that it prevents it

from spreading to other synapses, it prevents the excessive buildup of glutamate at that synapse that could lead to a cytotoxic death.

Q Okay. So it both protects that local synapse but also prevents the spread to other areas?

A And certainly it prevents waste.

Q Because it recycles?

A Yes, sir.

Q Now, "When the astrocytes malfunction or die, glutamate flow may become excessive, shifting the balance in the direction of overexcitation as well as suppressing GABA inhibition." Do you agree with that statement?

A No.

Q What about that statement do you disagree with?

A GABA is actually also dependent to some degree on astrocytes. If you don't have the astrocyte that's present, the formation of GABA, it may actually be too much that's there, too little that's there. It's making an assumption. GABA actually is only two steps down from glutamate, or actually GABA is made from glutamate. And therefore if the cell is making glutamate, it's also making GABA depending on the enzyme, and therefore, I think that statement is very

simplistic and somewhat an inaccurate representation of what actually happened in that local --

Q But it is one of it sounds like several outcomes that could be happening at that local --

A No, it's not. That's why I said it's not an accurate representation. It's much more complicated than that.

Q And the part that's inaccurate is the idea that as astrocytes die, it suppresses GABA inhibition?

A Yes. And also the astrocyte dies, but the problem with astrocyte death is that the glutamate doesn't stick around in the area, because as Dr. Kinsbourne identified, he says that one of the jobs of the astrocyte a few lines up is it blocks the extra synapse and spreads to other synapses. The glutamate may just drift away. It's not necessarily going to hang on just in that neighborhood, and if it drifts away, there is no glutamate.

And the problem is that if the astrocyte dies off, there is no source of the precursor for glutamate, for the neuron to do its job, so that whole system isn't going to work right period. It's not going to be a low level of hyperexcitation period of time. Again, that's too simplistic thinking. There are so many more things that may happen. I don't

believe that this hypothetical model would ever occur in reality because of all the other things that would ensue.

Q So that's why we'll talk about your conclusion that we will get to. I really want to walk through the specifics here. Now proinflammatory cytokines attenuate the astrocytic clearance of the extracellular or cellular glutamate, is that correct?

A Presumptively, I don't know -- functions, so I assume that this is one of the functions that might be modulated.

Q And then he goes on to say that astrocytes can release glutamate themselves. That's correct?

A Theoretically yes, they can release glutamate themselves in a neuromodulatory mechanism.

Q And then the interaction of the aggravated microglia can substantially amplify glutamate release from astrocytes. Do you agree with that?

A No.

Q Now that is something from published literature, so you disagree with the folks who wrote the paper there cited?

A Number one, I think it's taken out of context from the paper. If you have the paper, I'm happy to read it because I haven't looked at this

paper for quite awhile, but I'm happy to read it and tell you the context in which that statement was actually made.

Q The questions I'm asking are based on your knowledge stated here today to the best of your recollection, so if you can't recall the paper, that's fine.

A I think that that is not an accurate representation of what the paper is actually telling us.

Q And then he goes on to say that "Because of glutamate excess, adjacent circuitry becomes activated in a manner that escalates over time." Do you agree or disagree with that statement?

A If there truly is glutamate excess that's present, yes, and as I stated before, it will escalate over time to cell death. I agree with that.

Q Okay. And then the final part of his, and it's a quote from a paper, and I think that the paper speaks for itself and both sides are debating the significance or the conclusions one can draw, so I'm not going to ask you whether that is correct because again the paper is the paper. So we've walked through step by step your assessment and your critique, so to speak, of Dr. Kinsbourne's model.

Stepping back away from this glutamate-based model in a way, do you believe that there is any excitatory inhibitory process that's occurring in the brain?

A Well, everyone's brain has an excitatory inhibitory process. It's always present.

Q And will you agree that it would be a problem if, however it's caused -- we're not trying to talk about vaccines or any particular cause -- that if you have overexcitation of the brain, it potentially can present with neurological symptoms, things that would be clinically significant?

A Oh, yes. Neurological symptoms or signs to be exact. Symptoms may be subjective, dealing with the complaint that the person has. Sign is the physical manifestations that they show.

Q And whether symptom or sign, these would be things that would be clinically significant in some cases?

A Yes.

Q Now, given an excitatory process in the brain, overexcitation and a disequilibrium if you will between excitation and inhibition, if you assume that that has taken place, again not in reference to the cause because obviously we are not going to spend the

afternoon coming to an agreement of what might be causing these things, but given that state, would it be reasonable to think that a child in that state would avoid very stimulating circumstances in his or her life?

A No, I don't think that you can come to that conclusion.

Q Why is that?

A Well, you already mentioned to me that you have symptoms or signs, but there wasn't basically seizures. You basically have seizures. And we know that that happens, as I said, from unfortunate experiments of nature, that that's what happens when the GABA is out of whack.

And to my recollection, for children who basically get excessively distressed by the environment, this is not a model that to my knowledge has been proffered as the reason why the environment stresses them, and I think a good example of that is anxiety disorders, especially, for instance, you're asking about social contact and things of this nature, which would be an avoidance behavior. That's not a model that's been proffered.

Q The overexcitation model.

A The overexcitation model is not one that's

been proffered.

Q And in your experience and your familiarity with the literature, the overexcitation model applies primarily to seizures?

A To seizures. And the reason why Dr. Kinsbourne used his presentation and his hypothetical in this situation, the example he gave specifically was starring, the mannerisms or the self-stimulated, whatever terminology you wish to use for autism, and he stated that these behaviors are done because of overexcitation, and when they get overly excited, they do it more.

And it made me think back to my clinical practice and the complaints that parents have many times where the parents will say that the kids do it when they have nothing better to do, and actually if the parents were being more prompt or engaged them or if they are in an office and we see these kind of behaviors and I engage them, they stop.

But there I'm stimulating them by social engagement, the exact scenario that Dr. Kinsbourne said should provoke the behavior, but I stopped the behavior in that manner. The parents are able to stop the behavior, which means that from the clinical or functional standpoint, the model doesn't have any

legs.

Q And when you say that the parents can interrupt to change behavior, you're familiar with the presentation of symptoms of patients where children are nonresponsive to either clinical or parental intervention on things like self-stimulatory behavior?

A I mean, there are some children that have symptoms that present in a way that they are unresponsive and avoid contact with the person that's attempting to very directive behavior.

The issue in autism is simply that the social issue of autism is not avoidance of contact. That's not a core criterion. And if you look at the core criteria for the social deficit, avoidance of social interaction suggests more social anxiety I believe than the social behavior of a child with autism. In autism, it appears that they have little to no interest in social interaction.

But when I approach the child, the child is not interested in interacting with me. In fact, when parents say to me that when kids come in the room, my child will move to the other end of the room, I don't think of autism.

Q Now, in looking through your CV and looking through your list of publications and the abstracts, I

was looking to see if any of the papers in there were papers that were descriptive of causation of autism spectrum disorder. Have you published papers that address the potential causes of autism spectrum disorder?

A Probably within either my book chapters or one of the papers we wrote about the work that we would have a comment on attention causes when we're talking about diagnostic evaluation, and we also talk about the differential diagnosis.

Q Yes. Understanding that, have you done any original research investigating, so, for example, postulating or hypothesizing a potential cause of autism and then conducted a research project to test that hypothesis?

A No.

Q Have you ever worked on teams of people that have conducted research? Even if you haven't published, have you participated in that work?

A We have in a roundabout sort of way. We have studies done on preschoolers and then school-age kids to differentiate the features of autism and what we hope will be some of the core reasons on imaging and electrophysiology from children with medical retardation and children with language disorders.

Q Was your participation in that project to basically supply the subjects of the research?

A No. I actually ran the project, the second study, the school-age study. I ran that at the center. I was the local investigator that ran it. I also evaluated all the children, made sure all the data got submitted. The electrophysiology data, the imaging data, so forth and so on was submitted to the central study.

Q But nothing that generated a published --

A Oh, there were publications that came out of it. It's been so long I can't remember. I just know the most recent one was the one that's in my CV that David Mandelbaum was the first author. It had to do with sensory and other issues.

Q So that Mandelbaum paper went to issues of causation and ASD?

A I don't know if it went to causation there. There were other ones that explored that issue. I remember I was listed as an author, and I don't know.

Q And then just a few more questions. I know that you participated in the Cedillo case. You prepared an expert report and you showed up to testify. I know in this case, you've submitted two expert reports and obviously are here today

testifying. Have you participated in any other vaccine program cases involving autism aside from the Cedillo matter and this matter?

A Yes.

Q What would those be?

A Without giving names?

Q Yes.

A I can't do that. One was actually the question of the timing of onset of the autism.

Q How long ago was that?

A I think last year. And I think the issue that was there was more a legal issue of whether the submission for claim was too late.

Q The timeliness of the claim and onset of injury?

A That's beyond me. That's a legal issue.

Q Which side were you appearing for?

A I reviewed it on behalf of the government, and I know I have a few records at home of other children that I was told to stay my hand because I think they were put in the omnibus program, and I never even generated a report.

Q That's what I was going to ask, have you generated a report or testified. So you reviewed medical records or you have medical records that you

would be capable of reviewing. These were at the request of the government also?

A Yes, sir. And I would be happy to review for petitioners who have ever contacted me. I'm sorry. I am wrong. I got contacted by one petitioner attorney about the feasibility of actually filing, and they asked me to review the information, which included a videotape of the child, and then I gave a review.

Q And then finally, have you appeared in any civil cases involving claims of autism outside of this vaccine program?

A Yes. There was a claim, Doe v. I guess it was McNeil or Johnson & Johnson or one of those companies, that was in federal court in North Carolina.

Q Was that the Rhogam case?

A That was the Rhogam case where there was a claim of autism. It was a Daubert hearing. The plaintiff's experts were excluded by the Judge.

Q But my question is your participation, did you prepare an expert report in that case?

A Yes, I did.

Q Did you testify at depositions?

A I testified at a deposition. I must have

given a deposition because I know I actually testified in court, but I don't remember. Whether I gave a deposition, I don't remember, but I remember I testified in court.

Q And that would have been during the Daubert hearing?

A That would have been during the Daubert hearing, yes, sir.

Q And then aside from the Rhogam case, any other civil cases that you have been involved with where the claim at issue was autism?

A No, not to my recollection.

Q And then the North Carolina case, presumably you were an expert witness being paid by the drug companies that were involved or their lawyers?

A I don't remember which. I know I was contacted by the lawyers.

Q But the check did come?

A It did come, yes, sir.

MR. POWERS: No further questions.

THE COURT: One moment.

(Pause.)

THE COURT: Doctor, I don't know how much of this was mentioned but, let me try. You've described that in about 25 to 30 percent of kids on the autism

spectrum, we can identify some cause.

THE WITNESS: Yes.

THE COURT: Is that correct?

THE WITNESS: Yes, we have the test capabilities to show cause.

THE COURT: So we show that the child has tuberous sclerosis or we show that there is Fragile X or we show Rett syndrome or we show something like that.

THE WITNESS: Yes, ma'am.

THE COURT: Or we have a history of congenital rubella or a history of Thalidomide use in pregnancy?

THE WITNESS: Yes, ma'am.

THE COURT: And those children are all classified as having the same disorder, I won't call it a disease, the spectrum disorder.

THE WITNESS: They show similar clinical features.

THE COURT: Okay. And that's what I was working for.

THE WITNESS: Which really gets to the point if I may be presumptuous.

THE COURT: Go ahead.

THE WITNESS: What it really is, you're not

talking about autism, you're talking autisms. In other words, there are several ways to get to the same end result.

THE COURT: You are talking about a group of behaviors, some core behaviors must exist in each case in order for children to receive this diagnosis?

THE WITNESS: Yes, ma'am.

THE COURT: But there may be a wide variety of behavior outside those core behaviors. In other words, people may have some social avoidance. You can have two children, for example, that have the same core behaviors, but one might be on the -- end of it, that is, mentally, intellectually functioning well, and one might be -- one of the poor children with IQs of 70 or below?

THE WITNESS: Yes. And what happens there is if you actually look at those children, it doesn't matter if they have Asperger's Disorder or they have autistic disorder, say 50 because it's a nice, easy number to use.

THE COURT: Okay.

THE WITNESS: You're going to still find the same core deficits, but the manifestations are subtly different because it depends on their intelligence. They are both going to have issues with social

interaction, but I would expect a child on the lower end to have greater impairment, in other words, the quantity is more, not the quality, the quantity is more than a child with Asperger's Disorder, who still have a social deficit as described quantitatively. While it's still an impairment, it's not as severe.

If you come to my office and see the children march through, I mean, I can see 10 kids in a day and you will see different levels of social ability, but they are all significantly impaired in the same way. They have problems with initiation and maintenance of the social interaction. They have problems with the use of social abilities and social cues. There are not verbal aspects of language, of socialization, reading peoples' actions, reading faces, reading body language. It's not enough.

I mean, there are some people who just have no interest in socialization. The other ones when you approach them will interact with you, but they don't maintain interaction after you break off that social contact. But it's all within the spectrum of social dysfunction that we know occurs within the autistic disorders.

The reason is that just taking some -- all these problems are not only severity, but they are

also age-dependent, because I think you had asked that question does the brain continue to develop. Of course, it does, and therefore, the manifestation at two years is not the same manifestation that you would see in say seven years, but they are still going to show a qualitative impairment in socialization. Does that answer?

THE COURT: Yes, it gets me a little closer to where I am trying to go. When, for example, we have a child with Rett syndrome, a girl who engages in the hand-wringing that we see classically in Rett syndrome, and we have a child, let's say a boy who engages in some similar conduct, some stereotypic behavior with his hands, it may not be the wringing, it may be something else, we have two children who have diagnoses on the same spectrum.

We have a cause for one, and I use "cause" in the sense that we identify the Rett's child with a genetic defect, the specific genetic defect. And then we have a similar behavior by a child who does not have that genetic defect. Say it's a boy and we've tested him just to be on the safe side.

Well, from that, we know that something in the brain besides simply having this misformed or malformed or extra copies of the genetic defect is

causing the brain to develop in such a way that these children display the same or very similar stereotypic behaviors.

THE WITNESS: If I cannot use the Rett girl.

THE COURT: Okay.

THE WITNESS: Let me explain why. But girls with Rett syndrome are actually social, they are interactive. They are very friendly, and they all come up to me and they stare at me and they want to interact with me. They are just incapable because of their --

THE COURT: Sort of the eye expressive.

THE WITNESS: Yes, they are very expressive with their eyes. One of my patients now is in the hospital and one of the reasons she is in is because her behavior changed. We know she's sick, and we have to figure out why.

And the hand-wringing in Rett syndrome probably has a sensory base to it because when they wring their hands, you can measure EEG discharges. If you do some sensitive testing, there is some feedback that goes there and we don't quite understand what is it that drives that behavior, but let's just take a stereotypic behavior in children. They might have finger-flicking in front of the eyes.

I'm not presumptive enough to say because a boy does this and a girl does it that it's the same biologic mechanism. That boy may have a neurologic deficiency that's driving that behavior, and the girl may have tuberous sclerosis that's driving the behavior. We're just seeing the same physical manifestation for whatever reason that it occurs.

THE COURT: The physical manifestations we see, the signs if you will of behaviors, core behaviors of the autism spectrum, may have a variety of causes.

THE WITNESS: There is a variety of underpinnings, but it's probably somewhat similar areas of the brain that are dysfunction for driving it. I think, as Dr. Kinsbourne already stated, there were these very simplistic models in the old days that it's a problem with inflammation going from the brain stem up to the brain, the upstream deficit, but that was proven not to be true.

Then there was the downstream deficit and that was proven that it was too simplistic. Then there is the limbic system dysfunction, and that's proven not to be sufficient. And probably the prevailing model nowadays is the neuro network model that's been known for quite awhile. I have known

about it for about 10 years, but now it's becoming more familiar to the rest of the world.

What it means is that some of the nerve cells won't talk to each other and can't synchronize their activity taking simple things. For instance, I can move my finger, that's a simple thing, but to coordinate the whole hand use is a much bigger issue because they involve multiple areas of the brain working together.

And the same thing with social behavior. I might be able to see you, but the social behavior responding in an socially appropriate manner, which is a much more sophisticated thing, is a bigger problem. The simple test to be done is the more complex task that requires synchronization of the brain engines, of the neuro network. One, that's the impairment, and there are lots of ways of getting there, and there are lots of different things that you can interrupt with the appropriate formation of a neuro network.

The brain is very sophisticated. Just to give you an idea, I can interfere with dendritic development, which is the receptor side where an axon will end up. If that dendrite is not as well-developed as it should be, it's not going to function, and we see that in Fragile X syndrome where the

dendritic development isn't right. I may not be able to have good -- and it doesn't go where it's supposed to go, and we know that because of some of the neuroimaging work that's been done when you measure volumes and you look at things.

There may be issues where there is too much brain tissue, in other words, there are too many synapses that are present, and therefore, I call it too much static, and therefore, systems don't work right.

Someone mentioned mini-column yesterday. The mini-columns are the wrong size, and therefore, they are not doing the job they are supposed to do because the system wasn't built right.

THE COURT: And one thing doesn't have to cause that mini-column.

THE WITNESS: There are a lot of different reasons why that mini-column -- there is a lot of things that are -- let me give a simple example. The brain is too complex. In the heart development, there are oodles of different signals that are sent to the heart to develop, and if any of those signals go awry, you're going to get heart malformation. There are lots of different signals during brain development.

THE COURT: And that heart development could

happen congenitally?

THE WITNESS: It's only congenital. By the time you are born, the heart is developed.

THE COURT: All right. I'm getting at you may develop a valvular defect, for example, rheumatic fever.

THE WITNESS: Yes, that would be an acquired problem. But looking at the brain, there are lots of signals that have to be sent, and there has to be a cascade of signals. There is a sequence of signals that occur. Destruction of that sequence in different locations, for instance, in neurolike disorders, these are actually scaffolded in probes. These are probes that hole up into the nerve itself and it's supported. There are lots of different scaffolding probes, any of which if it's dysfunctional theoretically can lead to the same result. But that's predestined in terms of if you don't -- it's set up in that the signals aren't going to be sent.

And I think you used the example of Rett syndrome. The reticulars are doing perfectly okay, but signals aren't being sent right, and the signals do involve the Rett's picture because biologically you were predetermined to get there.

Fragile X, when we look at the kids, the

milder kids, initially you can't tell the difference. It's only as they get older that these features show themselves.

THE COURT: I recall reading a couple of case studies, and I apologize that I can't turn them off the top of my head here, but of individuals who developed autisticlike symptoms in adulthood. What's going on there?

THE WITNESS: Well, I think your wording is correct, ma'am. I think it's autisticlike, and the real question is if one of us came along with some of the DSM IV criteria and we rigorously applied it to that individual, would they actually apply?

THE COURT: Okay.

THE WITNESS: And may I explain?

THE COURT: Sure.

THE WITNESS: First of all, the one you're describing classically is individuals with herpes simplex encephalitis. It's a viral encephalitis. Big holes, big holes, anterior temporal holes are wiped out, don't make new memories. We know that because there is a congenital model, and I have a few patients with this.

THE COURT: Right.

THE WITNESS: And they are just

developmentally not right. When I look at these kids, they are autisticlike, but they feel different. Do you understand what I mean from a microcondition stand?

THE COURT: Yes.

THE WITNESS: They are not like the rest of my autism patients, but they manifest some of the behaviors. And I think we are seeing the same thing in here. Because of the damage, they can't process certain signals.

Another example would be if you develop an intractable epilepsy, or let's call it epileptic encephalopathy. There is a lot of static that's there, and people that use the determinative autism spectrum disorder features, the issue there is that the epilepsy all goes away. That's a superficial glaze. To me, actually they look dull and glazed. They are not bright-eyed and bushy-tailed like my typical autism patients. So there are subtle differences to me.

THE COURT: Although some of the behaviors are the same.

THE WITNESS: Some of the behaviors are the same, but they are not exactly the same. And that leads to the whole issue of how rigorous you need to

be in order to define things in the literature, and it was interesting. Dr. Zweiman's point is that it depends on the lab that runs the tests and the methodology as to how you are going to be able to interpret the information.

The same thing here. Medical Center A may have much looser criteria for defining autism spectrum disorder than Medical Center B even using standard tests, the ADI and the ADIS. I have seen individuals who had these tests electrically -- these scales filled out for them. Everyone agrees they don't have ASD, they have some other condition, but the individuals who used it were much looser in their criteria and inadvertently classified them that way until we were able to reverse it, and it was simple to virtually treat the underlying condition and make it just go away.

Therefore, I have to stick to my simple autistic, this kid has autistic disorder. Those kids are clear to define. When you get out to those borders, it gets a lot of controversy on how you define them.

THE COURT: So a finding that herpes encephalitis can introduce autisticlike behavior in an adult does not mean that it is a viral influence that

causes --

THE WITNESS: Oh, that's pure brain damage.

THE COURT: Okay.

THE WITNESS: It's not viral influence.

THE COURT: Okay.

THE WITNESS: If you read the articles, they will tell you.

THE COURT: Yes.

THE WITNESS: That's actually what these individuals are left with. They are left with assistic encephalable dysplasia, just holes where brain tissue used to be.

THE COURT: And I understand that. What I was getting at, however, the point I'm trying to understand is that the behaviors that people with autism demonstrate, those behaviors can be mimicked in some way by people who do not have autism, and I'm not making it clear.

THE WITNESS: Let's take the epilepsy.

THE COURT: Okay.

THE WITNESS: Epileptic encephalopathy kids who even though they classify them as having it, I don't think they really do. They can be mimicked by things that adversely affect the brain, yes.

THE COURT: Now let's move to strict autism.

We're not talking about these behaviors that mimic it. Within autism, you've talked about the classic autistic child, the regressed autistic child, and you recognize, do you not, that there are differences or do you not recognize differences?

THE WITNESS: Differences of?

THE COURT: Well, in terms of how the disease manifests and the prognosis for the children.

THE WITNESS: Yes. Well, if I will take a child with classic autism and I will take a child with regressive autism at two and a half years, they will be exactly the same. That's why it's important to have a history. And I think you are right, prognostic is --

THE COURT: And then at age 10, how are they going to look different?

THE WITNESS: The children with regressive autism classically don't do as good. They just don't do as well. That's the traditional teaching. The children with regular autism, the children still don't do well. I mean, you only have less than 10 percent who will have a functional outcome even though about 30 percent will probably have normal intelligence but not enough to have a good functional outcome. Do you understand what I mean by that?

THE COURT: I do. I understand.

THE WITNESS: Because the autistic features may be of sufficient severity even in an individual with normal intelligence to function adequately in society.

THE COURT: Someone can sit in a room and calculate prime numbers but can't manage to make dinner for himself?

THE WITNESS: Yes, ma'am.

THE COURT: Okay. And we do not know anatomically, brain anatomically, what differentiates that classic autistic child from the regressed autistic child?

THE WITNESS: No. First of all, we don't even know if there is a difference. We don't have enough information. For all I know, their problems are the same. There are different ways you can build up models. One model will be that you're talking about two totally different conditions that perhaps affect some different areas of the brain and manifest at different times.

Number two is that the problem is in the same areas of the brain, but just whatever goes awry goes awry later in the regressive form compared to the classic autistic form of their symptoms. They are

easily identifiable at 12 to 18 months, and when you look at them, you will see that there were issues that were present, and that's why I was stating that in reading the more recent literature, people are raising questions that in these children with regressive autism at least some of those kids have more than a common disorder.

It might contra the energy boxes in the cell, and if you have a battery in your flashlight, it may die tomorrow, it may die in two weeks or it may take a year to die. It depends on when the battery dies. The same thing as the energy boxes not working right. They can function mechanically up to a point and then get overwhelmed with demands and the cell dies.

And it's believed that at least a group of regressive kids have some sort of mitochondrial dysfunction that produces this regression where previously he looked okay. I think that is a biologic possibility because that makes sense because it fits the other mitochondrial disorders we see, but it gets percolated. If you don't mind my giving you an example.

THE COURT: No, go ahead.

THE WITNESS: I admitted a girl to the

hospital last week. She has a family history of mitochondrial disorder. She was actually doing pretty good. Then if you examined from a neurology standpoint, the girl's examination was good until she had her first stroke at 19 years due to the mitochondrial disorder. Now she has balance issues and such, but we know the genes. It just took awhile for her gene to express itself. There was no outside influence. This is just the way in her it happened, and it has to do with how much of the mutated genes, mutated mitochondria in the cell, how much normal mitochondria in the cells as to when things will prove up and lead to problems.

Yet her cousin, the same genetic predisposition but a much more adverse mitochondrial load of mutated mitochondria, we weren't able to test it, presented in the first few years of life with scrofula and unfortunately subsequently died. It's the same condition that has variability in presentation. That's just to give you one model of what may be causing the regressive. We just don't know the rest.

THE COURT: Questions, Mr. Johnson?

MR. JOHNSON: I actually just have one.

//

REDIRECT EXAMINATION

BY MR. JOHNSON:

Q Doctor, on cross-examination when Mr. Powers was asking you about Dr. Kinsbourne's theory or his hypothesis and there was a sentence that related to the depletion of purkinje cells in the brains of autistic individuals, how that may result from cytotoxic effects of the excess glutamate, you used the term "presumption" with respect to that, and I just wanted to make sure that you were saying that that was Dr. Kinsbourne's presumption and not your presumption.

A No, that was Dr. Kinsbourne's idea or hypothesis that has been represented by cytotoxic effects, not mine.

MR. JOHNSON: Okay. Great. Thank you.

THE COURT: Mr. Powers?

MR. POWERS: Nothing further, Special Master.

THE COURT: All right. Thank you very much, Dr. Wiznitzer.

(Witness excused.)

THE COURT: Given the time, do you want to go ahead and start with your witness?

MR. MATANOSKI: Yes, ma'am.

THE COURT: Okay.

MR. MATANOSKI: I think it will take a few minutes to get him set up.

THE COURT: Not a problem. If you want to just take a very quick five-minute recess.

MR. MATANOSKI: That's great.

THE COURT: All right.

(Whereupon, a short recess was taken.)

THE COURT: Let's go back on the record in the Snyder case, and we have I believe Dr. McCabe on the stand. Dr. McCabe, if you would raise your right hand.

Whereupon,

MICHAEL J. MCCABE, JR.

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

THE COURT: Please be seated.

You may proceed, Mr. Matanoski.

MR. MATANOSKI: Thank you.

DIRECT EXAMINATION

BY MR. MATANOSKI:

Q Good afternoon, Dr. McCabe. Let me just say that you're going to need to speak up. I don't think that will be a problem for you. The pickup on the audio is pretty good in this courtroom.

Could you state your name for the record, please, and spell it also?

A Michael Joseph McCabe, Jr. Last name is spelled M-C, capital C-A-B-E.

Q And what is your position and area of expertise?

A I am an associate professor in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry. My area of expertise is in immunology, immunotoxicology.

Q Have you ever testified before in a lawsuit?

A No, this is my first time.

Q Welcome. Could you please explain or just give us a brief overview of your educational background, starting with your undergraduate education?

A Yes. I received a Bachelor of Science in biology from Siena College. It's a small college outside of Albany, New York. Then I went on to graduate school starting in 1985, completed my thesis work in late summer of 1990. My actual Ph.D. Degree was awarded in 1991 in microbiology and immunology, and that was at the Albany Medical College, also in Albany, New York.

Q And did you go anywhere after that for more

advanced training?

A Yes. So starting in the fall of 1990, I traveled across the great pond to Sweden, did a two-year postdoctoral training period at the Karolinska Institute.

Q I'm just going to stop you for a second. I probably warned you a little too vigorously about good pickup. You need to step back from the microphone a little bit.

A Right.

Q You were telling us about the Karolinska Institute.

A Yes, I did. Now is it?

Q Well, I think it's somewhere between the two. A little closer but not too close. That's just right.

A Just right. Is that good?

Q That's good.

A So yes, I did a two-year postdoctoral, a fellowship with the Karolinska Institute, which is a university located in Stockholm, Sweden.

Q What kind of work do they do at the Karolinska Institute?

A It's a major, just like any American medical center, medical college. They do all sorts of work.

What attracted me to go there was I was interested in a particular area of research known as apoptotic cell death, and there was a leading laboratory located in Stockholm doing this sort of work, and that's what attracted me there.

Q And following your sojourn to Karolinska Institute, where did you go thereafter?

A In the fall of 1992, I came back to the United States and started my first academic position as a faculty member at a placed called the Institute of Chemical Toxicology located in Detroit, Michigan.

Q Probably appropriate place, and New Jersey.

(Laughter.)

A I was there for seven years, advanced from the rank of research assistant to assistant professor.

Q And after your stint at that location, where did you go next?

A In 2000, I was recruited to the University of Rochester, the Department of Environmental Medicine. I've been there ever since.

Q What is the field of immunotoxicology? Could you describe for me what it is?

A Sure. Immunotoxicology, as the name implies, is the merger of two disciplines, immunology and toxicology, and the scope of that area,

particularly subdiscipline research, involves research involving examining adverse effects of environmental chemicals, occupational exposures, drugs, other immunomodulators on immune response. The scope includes issues relevant to mechanistic research to understand how these agents work, to exposure assessments, risk assessments to try to understand how can some of this work be extrapolated, translated into issues relevant to human populations.

Q When did you begin your work in the field of immunotoxicology?

A I think I began my work in the area of immunotoxicology when I was in graduate school, whether I realized it or not, and I say that because I went to Albany Medical College and was working in the Department of Microbiology and Immunology. I was attracted to that particular department because I wanted to receive training in cellular immunology, so I think I was trained as a cellular immunologist.

I was working in the lab, interested in the effects of heavy metals and the use of heavy metals as tools to modulate effects. It wasn't really until I came back from the Karolinska and started working at my first faculty position charged with deciding what I want to be when I grew up, and write my own grants and

start writing my own lab that I think I stepped and thought this would be a niche based on my experiences.

Since I had been trained as an immunologist, it would be an easier fit for me to work in the area of immunotoxicology trained as an immunologist rather than trained as a toxicologist. So that's essentially where things started.

MR. MATANOSKI: This is not directed to you.

I have to apologize for the record because I just realized that Special Master Hastings is sitting here, and I made that offhanded comment about Detroit.

THE COURT: You forgot that I too grew up --

(Laughter.)

MR. MATANOSKI: Now I'm in trouble. I hope you're not about to entertain a motion at this point.

THE COURT: The Michiganders will be visiting you.

(Laughter.)

BY MR. MATANOSKI:

Q Doctor, I'm sorry for that side comment.

Right now working in the field of immunotoxicology, you are in the department -- what's your posting right now at the University --

A Department of Environmental Medicine.

Q What work does that department do?

A It's a relatively small department. There are around 10 to 15 investigators researching in a number of different areas I would describe as areas in neurotoxicology. University of Rochester and its department has a longstanding expertise of investigators in that particular area. We have interests and faculty working in the area of immunotoxicology. Those are my colleagues. They are all my colleagues.

But we have a group interested in osteotoxicology, influences of toxic chemicals on bone. This is probably the only group in the country working in that area. And we have another group interested largely in pulmonary function, pulmonary biology, pulmonary toxicology, particulate matters and things of that nature.

Q What attracted you to the University of Rochester?

A So in addition to a longstanding program in neurotoxicology, and I should also mention the pulmonary group has historically been strong at the University of Rochester, the immuno group, the osteo group are merging within the department at the university. But the University of Rochester has had longstanding expertise, investigators working in the

area of metal toxicology.

Also in the last few years, the last decade or so, the immunology group at the University of Rochester has become very strong, stronger. I think it would be a detraction to infer that it wasn't strong prior to that. But it's a very strong group of investigators working in the area of immunology.

So remember I told you that my area of expertise is immunotoxicology with a particular emphasis on metal toxicology, so coming to a university and having colleagues that I could talk to about issues of metal toxicology as well as issues relevant to immunology made it an attractive place for me to be.

Q Do you teach in your current position?

A I do.

Q What do you teach?

A I teach several areas to graduate students, topics related to metal toxicology, topics related to immunotoxicology, so topics related to my expertise. I lecture on autoimmunity, introductory lectures on autoimmunity to toxicology graduate students. I lecture to medical students on issues relevant to lead toxicity and lead poisoning. I also run a colloquium-style course that comes up as an elective for graduate

students in the spring every other year, and that's a topics survey course in the area of immunotoxicology, so this is a paper discussion type course with graduate students. That's usually a lot of fun, a lot of back and forth on that type of venue, different than deductive lecturing.

Q Do you run any laboratories?

A I do. I run my own laboratory, and I am the principal investigator and chief of that laboratory.

Q And what work does that laboratory do?

A We work in the general area under the umbrella of metal immunotoxicology. We have several projects ongoing. So my background interest has always been in lymphocyte activation, lymphocyte signaling modeling. So as you heard from the testimony this morning, lymphocytes, B-cells and T-cells are the cells that are mainly responsible for adaptive immunity.

So my longstanding interests, I am trained as an immunologist, have been studying and understanding signal transduction about the guard and function of these cells, the signal transduction being how is the information transmitted from outside the cell through the biochemical reactions that allow information to be transmitted from outside the cell

into the cell, to the direct cell to express the genes to divide, to differentiate.

So my lab has been interested in how are these processes modulated by exposures to metals, how we can use metals as tools to provoke changes in these signaling patterns.

One project in particular focuses on mercury and it analyzes how does mercury interfere with T-cell syndrome, how does it interfere -- first of all, does it, and it does, and how does it interfere with depth receptor signals, the processes of physiological cells that are still working in the immune response.

Another project with arsenic deals with understanding how arsenic modulates the cell cycle. Arsenic is used as a chemotherapeutic agent, so we're interested in how does arsenic dysregulate the control cell.

Q How is your time divided between the various duties at the university?

A I would say I spend about 50 percent of my time as a researcher. Unfortunately, as I've progressed, that time as a researcher is not spent in the laboratory at the bench but still as a researcher in terms of reading papers and writing papers and writing my own grants and designing experiments,

things of that nature.

About 15 percent of my time is spent teaching as I described to you. Another 15 percent of my time is spent on administrative duties, other scholarly activities, going to meetings both within the building and outside the building nationally, reviewing other peoples' work, reviewing manuscripts and grants.

Then I would put a category -- if I'm following my math in my head correctly, it should add up to about 100 percent -- about 20 percent of my time is spent mentoring graduate students, postdocs, technicians, and that mentoring crosses teaching responsibilities because it's a form of teaching, but it also crosses research because it crosses into the research realm as well.

Q Just cleaning up and then we'll go forward from educational, let's talk about some of your professional involvements. Are you on the editorial boards of any journals that would be appropriate to the issues we're discussing here?

A Yes, I am. I am associate editor of Toxicology and Applied Pharmacology. I'm also on the editorial board of the Journal of Immunotoxicology.

Q Just a second. You said associate editor

and editorial board. Is there a distinction?

A Yes. I've been on the editorial board of the Toxicology and Applied Pharmacology since late 1990s, and I believe it was in 2002 I was invited to be associate editor. So it's a peg up from the editorial board.

Q I see. I'm sorry.

A And the importance of that is that Toxicology and Applied Pharmacology is one of the two, arguably one of the two leading journals in toxicology. I am also a member of the editorial board of a newer journal called the Journal of Immunotoxicology, a more specialized journal. And just last week, it's not on my CV because this just happened, I was invited to join the editorial board of Toxicological Sciences, and I'm very happy to do that, the reason being that Toxicological Sciences is the second, arguably the second of the two leading journals in toxicology.

Q As part of your work on the editorial board of these journals, do you work as a peer reviewer for any special journals?

A Yes, I do. I review papers, peer review manuscripts for about a dozen different journals, probably on the order of about one a week, so it comes

out to be 40 or so a year. I get a few breaks every now and again. A few of them of relevance in addition to the three journals that I have already mentioned I of course review papers for. I also review papers for toxicology letters, other toxicology journals. I review papers for the Journal of Immunology, Environmental Health Perspectives on parthenogenesis as examples.

Q And are you a member of any national or international special organizations that deal with immunology and toxicology?

A Yes, I am.

Q It's probably listed on your r,sum,. Why don't you actually just tell us a couple.

A A couple of them. So one that comes to mind, currently I am on a National Academy of Sciences National Research Council Committee charged with establishing a safety standard for beryllium exposure, beryllium being an important metal of occupational relevance. In August of 2005, I was on a U.S. EPA panel charged with reviewing documents establishing air quality criteria for lead. And I've been on numerous NIH, National Institute of Health and National Institute of Environmental Health Sciences grant review panels.

Q Now this question when I ask it, sometimes it's a little -- I'm going to ask it a certain way that may make it a little easier.

Of the awards that you've received or the honors you've received, can you just list the ones that you are most particularly proud of?

A In 2000, I received an award from the Immunotoxicology Specialty Section of the Society of Toxicology. It's an award known as the Young Outstanding Immunotoxicologist Award. I am particularly proud of that award for two reasons.

The first is that was the first year that that award was given, so I took some pride knowing that there were some of my peers waiting in the wings and I was selected first, and so it was a Sally Field moment, "They like me."

And the second reason being at the age of 38 it was a "young" outstanding investigator award, so that's the reason for that. And I have the plaque on my wall still.

Q To remind yourself that you're young.

A I'm young at least at heart.

Q Have you ever been invited to present at national professional meetings on immunology?

A Yes. I've presented my work. Every year I

go to the annual Society of Toxicology meeting and present my work in some form, whether as a poster or as a platform presentation. On a number of occasions, I've presented at symposia. I've been invited to institutions around the United States to present my work in departmental seminar series and so forth.

Q And with respect to what you have contributed to the literature in the field of immunotoxicology, can you give me an estimate of about how many papers you have contributed?

A I would have to look at my CV. The majority, if not all, the papers touch on topics dealing with, directly dealing with immunotoxicology or related to toxicologies. So it would be 35, 40 papers.

Q We'll turn now. We're shift focusing again and now we're going to shift to your report that you prepared in this case, and I just want to briefly touch on your comments about Dr. Byers in the report.

Now most of the statements are fairly straightforward in this report. There is one that I want to draw your attention to to explain what you meant by that statement, and that is in your discussion of T-cells and T-regulatory cells in particular, you described what Dr. Byers was saying

with respect to that as "highly provocative." What did you mean by that?

A Yes, I did, and what I noted from Dr. Byers' testimony, that in addition to the comment about the regulatory T-cells was her comment that she was astonished by the number of papers dealing with the topic of mercury in the immune system.

Keeping in mind that this is the area that I work in and this is the literature that I -- I wasn't astonished by it. This is the literature that I contribute to. This is the literature that I read. These are the grants that I review prior to those papers coming out and being published. These are the papers that I download to my laptop and they're scattered over the desk in my office, so I have a pretty good handle on what the literature is in this area.

The statement that she made about the T-regulatory cells is provocative because you have to understand that T-regulatory cells are an emerging population of T-cells, emerging in that it only started to be discussed in the last five, six, seven years, provocative because it turns out that these T-regulatory cells are very important in or appear to be very important in controlling autoimmune diseases, at

least one mechanism that controls autoimmune diseases as well as other hyperresponses or hyperactivities in the system, including asthma and allergies. So there is great interest in mainstream immunology in this topic of T-reg cells.

So I think any time in this discipline that there is an intersection, this discipline being immunotoxicology, but there is an intersection of toxic agents on an emerging concept in immunology, that's a pretty hot topic. It's a hot topic in immunology. It's something that's discussed in immunotoxicology circles.

So if there was a sizable literature, I think any literature on mercury specifically targeting these T-reg cells, I would know about it, and these papers just do not -- there are no papers that specifically say that mercury targets T-regs.

Q On that same theme, in another part of your report, you essentially say there is no literature to support her statement that mercury influences autoimmunity, causes autoreactivity in T-cells in humans.

A That's correct.

Q And I believe you have taken, in fact, I know that you have a number of areas of dispute with

Dr. Byers with respect to the studies that she was looking at, but I believe you synthesized your main areas of dispute with respect to one issue in particular that you wanted to discuss here today, and that would be --

A It would be our slide 2.

Q If we could go to slide 2.

THE COURT: And when we say slide 2, you're referring to Respondent's Trial Exhibit No. 3, page 2.

THE WITNESS: Correct.

MR. MATANOSKI: Yes, ma'am.

THE COURT: All right.

BY MR. MATANOSKI:

Q Could you turn to that, Doctor, and could you tell me, please, what you were trying to discuss there with respect to your concerns about the use of this literature that Dr. Byers had put forward?

A In my opinion, I felt that Dr. Byers failed to understand. She is correct, there is a sizable literature that reports on mercury modulating the immune response in animal models. Individuals who are working in that area are interested in using mercury as a tool to cause the immune modulation to study immune modulation. It's the outcome that they are interested in.

Remember that I told you earlier that the scope of immunotoxicology encompasses research. It encompasses research that can be applied to risk assessment issues. The people who are working in the animal models, the mouse models of mercury modulation of immunity, their work cannot readily be applied to risk assessments, and I think Dr. Byers didn't have an appreciation for that. She had an appreciation of the outcome. It's the attributes of the disease that are being studied. The individuals who are working in this area are well aware that they are using very high doses of mercury to elicit these changes.

Q They are interested in studying, as you say, the immune condition that they've created. They are using the mercury as a means to create conditions they can study the immune conditions.

A Exactly. And the reason why it's a relevant model outside the realm of risk assessment is because it's an inducing model. It's not a genetic model.

Q Okay. Now you mentioned dose with respect to that, high dose. What kind of doses are we talking about here that they are using in these mouse models?

A Page 2 provides -- this is essentially in a lot of papers where the approaches are similar, and it's a model of mercury and immune disease where the

dose of mercury, and if I'm talking too close to the microphone, how is that?

Q I think it's because you get close to the microphone and you get more interested in the topic. But when I get off talking about your qualifications and started talking about immunotoxicology, you started zeroing right in on the microphone.

A In these studies, the approach is to inject mice with relatively high doses of mercury. You see there is a dose here of 1.6 milligram or kilogram. This dose typically is given subcutaneously to mice two or three times a week over the course of four weeks to 10 weeks, depending on the particular study that's under investigation.

This graph takes a conservative approach. It makes an attempt to take the toxicology -- remember we're talking about immunotoxicology here, so just take the toxicology component, how much mercury would an 11 kilogram child at 15 months need to be injected with over a four-week period or how much would that be over a four-week period twice a week. So it's a conservative application, extrapolation of what's in the literature for the animal study and then comparing that to what they were exposed to for vaccination over the course of the first 15 months of life.

So it's a comparison if I remember correctly. For vaccination, it's around 122.5 micrograms of mercury in Thimerosal in comparison to 1,000-fold to translate from the mouse studies.

Q So, in other words, the mouse studies that she is looking at the dose there were essentially 1,000 times the dose --

A That's correct.

Now, before we move on here, just remember again to be careful to talk about the immunotoxicology. What I mean by that is here I've just offered an intellectual exercise that gets at the issue of the toxicology, the dose of mercury. I wouldn't accept even if exposed to human beings to this high level of mercury that we use the same features of the disease that we see in mice. It simply has not been shown.

Nor would I accept that over a long period of time where an even lower dose of mercury in sensitive populations, what it means, that it would elicit the features of the disease. Again, it just simply hasn't been shown in human beings.

Q Now turning to Dr. Byers' discussion, she did discuss the study by Goth, and you focused on that paper in your expert report. I understand that that

is a particular area of interest for you, what Dr. Goth is doing. Could you explain?

A Yes, I can explain why I'm interested in it and in explaining why I'm interested in it hopefully captures the appeal of this study.

Interested in it because, as I told you, I have a longstanding interest in signal transduction, and Dr. Goth studied calcium signals as proven by ATP as an agonist to elicit a change in the signaling pathway in dendritic cells. So it's an in-vitro approach to examine the signaling pathway and show that it was modulated by Thimerosal.

And I'm interested in that because I'm generally interested in signaling pathways, particularly interested in it, including calcium signaling pathways, and in fact have been doing research on examining influences of inorganic mercury on lymphocyte signals.

What was important in that study and that the senior author, as you mentioned, is Isaac Pessah at the University of California at Davis, what was done that was important in the study was to link these changes in signal transduction, those changes in signal transduction elicited by Thimerosal to a change in cellular function, which was production of

interleukin 6, a single cytokine. Goth linked A to B, and what was novel was --

Q In-vitro?

A In-vitro. And what was novel was that it was dendritic cells. We have known for some time that Thimerosal provokes changes in calcium and other types in other studies in-vitro. Again, remember that I told you that we could use many of these chemicals as tools. Thimerosal proves to be a good tool to elicit changes in intercellular calcium, and we've known that for sometime. That was not new in Goth's study. He showed it -- I have to apologize, I don't even know if Goth is a he -- showed it in dendritic cells and linked A to B.

I commented on it from Dr. Byers' testimony because from my reading of what she was doing, she was linking A to B to Z, and to me as a scientist, I'm not quite ready even to go to C. I accept the limitations of the model, the in-vitro model that Goth and colleagues were using. So what might seem like B, show me that these changes in interleukin 6 production have any outcome. Often cytokines are produced in abundance. You may lower the level of cytokine, but does that lowered cytokine level have a physiologic function or an immunological function.

Show me that this modulation in cytokine production, in calcium signaling in these dendritic cells results in these dendritic cells, even in a more complicated in-vitro system where you take dendritic cells and mix them with T-cells.

You remember we brought in the testimony of Dr. Zweiman this morning that dendritic cells are antigen-presenting cells. They initiate the immune response or they present antigens to T-cells. Show me that in a more complex in-vitro system. Translate that into an atom system. Translate that into human beings. Put all of that in perspective of a human disease, and then we start to change from A to B to C and D and E, but you can't get there by ignoring all the letters in between.

Q Are you aware of any evidence regarding the notion that exposure to mercury would inhibit an immune response to a measles vaccine?

A I'm sorry. Can you ask me that question again.

Q Sorry. Are you aware of any evidence that would indicate that exposure to mercury would inhibit the immune response to a measles vaccine?

A No, I don't.

Q Now shifting focus again, turning to the

medical records in this case, did you review the records of Colten Snyder?

A Yes, I did.

Q And turning now to Dr. Bradstreet and his report and testimony. Since you are involved in immunotoxicology, I don't expect you to step out of that. Dr. Bradstreet talked about certain tests that were done with respect to mercury in Colten Snyder, and I would like to take you through those tests and have you comment on them, please.

The first such test -- well, it looks like I guess you would classify four different category of tests that were done -- blood, hair, urine and porphyrin. Let's take the blood first. Can you tell me what you can with the blood tests that were done with Colten Snyder?

A If you turn to page 7, you can see that over the course of six and a half years, this table captures three of those categories that you just mentioned, mercury in hair, urine, and blood. On five occasions, blood samples were submitted to the lab, and on each of those occasions, the findings were that the mercury level in the blood was essentially normal in comparison to the reference range. Colten Snyder's blood mercury levels were normal in comparison to the

reference range and oftentimes on the low end of the low end of the normal spectrums.

Q What does that tell you? It doesn't tell you anything necessarily?

A It tells me on those days, over the span of six years or more, on those occasions, he had a normal level of mercury in his blood.

Q You were here to hear the testimony of Mrs. Snyder in terms of the dietary intake?

A Yes.

Q Was there much mercury mentioned in the dietary intake?

A I'm not surprised that these levels are low. The level of mercury they received via vaccination is low, and as Colten's mother testified on Monday, she doesn't eat fish, which would be a main dietary source, maybe environmental source of exposure to methyl mercury and mercury, and so I'm not surprised that the levels were low.

Q I don't think those were discussed very much by Dr. Bradstreet, so we'll move on to something he did spend a little bit of time on, and that was hair tests as a measure of mercury. We had a little discussion on that I believe, and Dr. Bradstreet, there were some questions asked of him.

First of all, can you tell us what does a hair test for mercury measure? What does it actually measure? Just to direct your comments a little bit, it seems to be postulated by Dr. Bradstreet that hair can measure body level of mercury and perhaps the excretion of mercury, whether the body excreted mercury properly. Now what does the measurement of mercury in hair tell you?

A The measurement of mercury in the hair is a measure of exposure to an organic form of mercury, either methyl mercury or ethyl mercury, typically not falo (ph) mercury, there is another form of organic mercury, falo (ph) mercury that is usually metabolized so quickly that it's not found in hair. So you're talking about organic mercuries, methyl mercury, ethyl mercury. Thimerosal, for example, can be metabolized to ethyl mercury, so you might expect ethyl mercury to be found in hair.

It's a proxy for mercury found in blood at a particular time. What do I mean by that? Well, remember that hair in some people, not me, grows at about a rate of 1 centimeter per month, so you sample the hair strands, maintain the orientation of that hair strand so that you know which end came proximate to the scalp and which end is distal to the scalp, and

then you can measure the mercury content of the hair. Typically, because of issues, haircuts, things like this, you'd be interested in seeing the hair that's proximal to the scalp, and it gives you a proxy for measure mercury in blood at that particular time.

Now remember that hair grows, then you extend from that, and based on how far you go down on the hair strand, you can get an assessment of historical exposure.

Q Is hair a major source, major route of excretion of mercury from the body?

A It's a route of excretion, but I don't think it's a major route of excretion.

Q How are organic mercuries excreted from the body?

A Typically, they are excreted in the feces. They also undergo what's called enterohepatic circulation, and through that process, the organic mercury is converted to an inorganic form of mercury that can then reenter the bloodstream and then be excreted via the kidney. To be clear on this, the mercury that you find in hair and other sites of characterization, fingernails and toenails, is an organic form of mercury, because the methyl mercury sistine complex mimics amino acid, carotene being a

protein that puts a high demand on amino acids, and that's why the organic materials appear in these carotene places.

Q So, if I understand what you've been telling us, you look at hair. It's almost like a history to take a strand of hair.

A It can be used as a history. That's not always the approach that's taken. Oftentimes it's used to just give an indication of recent exposures. And if I could just --

Q Sure.

A It's well standardized. We have good reference values that we can then relate that hair level to blood levels of mercury.

Q So it relates to blood levels too?

A It's a proxy for blood levels of mercury.

Q And does it tell us anything about necessarily what the body level of mercury is?

A Not necessarily. It tells us -- at that point in time.

Q What point in time?

A Which that hair sample is representing. If it's close to the scalp, then it's within the last month or so. If it's more distal, then there are calculations that would be made to try to determine

where in time are we talking about. So it can be used as a measure of acute exposure. It also can be used as a measure of -- which I think is the main reason -- it can also be used as a measure of the steady state distribution of mercury between the tissues and the blood.

Q Now the last area -- well, actually you've compared the slide I believe.

A I did want to turn to page 3 if I could.

Q Yes. We prepared a slide about what the values were, and page 3, that's the Great Plains Laboratory value for mercury. Now Dr. Bradstreet, as I recall this, he stated he was surprised that this was a low value. That was his view, and I guess it is low on the reference range there, within the normal range, right? Could you comment on the absolute, in absolute terms about these values?

A I'm not sure if I understand what you mean by "absolute values," but I will tell you that I agree with Dr. Bradstreet's interpretation that this is a low value for mercury in hair based on the test results. Every indication here, as you prepare that mercury value of .1 part per million to the reference range, based on what I know about other reference ranges and other laboratories and what we expect, that

is indeed low. So I agree with his interpretation of this particular data set.

He also noticed there is a variety of other metals that are being analyzed here, but let's just focus on mercury because that's what's at issue here.

If we turn to the next page, page 4, I have prepared somewhat of a yardstick to place this all into perspective. So I agree with Dr. Bradstreet's interpretation. What I don't agree with is that Dr. Bradstreet indicated that he was surprised by this outcome, and I'm not surprised at it. Again, there is no mercury going in. There is no exposure to mercury, appreciable exposure to mercury via the diet as far as we know from eating fish, and the dose of Thimerosal is not adequate to produce a high mercury content in hair.

Q And just to that last point, the dose of Thimerosal, how many years are --

A If I remember correctly, Colten received his MMR when he was 15 months old, so that would have been in April of 1998, so two years before, and all other vaccines that contained Thimerosal would have been prior to that event.

Q Now, just getting back to hair, it's a measurement of mercury in the circulating blood,

correct?

A Correct.

Q And it's based on where you're sampling the hair from what time you're looking at in terms of the circulating blood. So unless you are looking at it I guess two years ago, for example, talking about Thimerosal, it's not really relevant to what you're talking about and understanding?

A That's correct. So it's not a measure of excretion of mercury into the hair. It's reflective of what we have already seen in the blood data. All right, the blood data, hair is a proxy for mercury in blood. There is low levels of mercury in the hair. There is low levels of mercury in the blood. The data match. There is no mercury going in as far as we can tell, and so the data match.

Q Now, on this chart, you've plotted out some other values. These were taken from other references I take it primarily.

A That's correct.

Q On that chart, I want to draw your attention to the 90 percent by U.S. children.

A Yes.

Q That's an average of what you would find in mercury -- U.S. children, do you know what age range

this was?

A It's not average, it's 90th percentile, and it's from a study of U.S. children. I believe the age ranges of those children were six to eight years old.

Q So in other words, in that study, 90 percent of the U.S. children --

A .4 parts per million are below.

Q Ninety percent of children in that age range had .4 parts per million. And on the high end, you listed some, another exposure of --

A The Iraqi Grain accident of the 1970, is that what you're referring to?

Q Yes.

A I'm orienting myself to what you mean by high. I would call it wicked high just so you know.

Q A common New England term.

A Yes. So yes, and I believe we heard about this through the transcript from the Cedillo case. Dr. Aposhian mentioned this and putting this in perspective. It was an unfortunate accident that occurred in the 1970s where the grain, the seed was coated with methyl mercury as a preservative. The intent was to plant it, but the grain grew, and unfortunately the people were hungry and they ate what was sent to them, and so it's a massive exposure as

you can see by this chart, exposure to mercury.

You also see a peg down a value of 170 parts per million. These are typical values that you would find in sustenance fishing, people who eat extreme amounts of fish or have extreme amounts of fish in their diet. And the point to make there is that it's a dose issue again, right. Those are the extremes of what we see in rare occurrence in select human populations. The majority of people as you can see at the bottom there, right, are down much lower, and a point to make is Colten Snyder based on his hair analysis is down on that.

As we walk up the yardstick, we can see that the majority of people, there is a very tight distribution of the amount of mercury you would expect to find in hair, anywhere from undetectable to 1.5 parts per million. Dr. Bradstreet indicated that he expected Colten's hair levels would be one, maybe 10 parts per million, and I took note of that. I just didn't expect -- I was surprised that that was his expectation.

Let me tell you about 10 to 20 parts per million. Ten to 20 parts per million based on some ongoing epidemiological studies, which is the Seychelles studies, also the Faroe Island studies,

these are

studies examining nerve behavioral outcomes in children whose mothers are eating large levels of fish and in some cases may produce hair mercury levels again reflective of the mercury found in the blood, in the 10 to 20 part per million.

The issue of 10 to 20 as you see as I've written here is that that's where we begin to be concerned about neurological deficits due to prenatal exposures. Ten to 20 means about a 5 percent increase in risk of some cognitive defects. High-level exposures in sustenance fish, the Iraqi Grain accident in the '70s, different story. That's just toxic.

Ten to 20, you see more subtle effects, but the issue is that it's mom's exposure. These are levels of mercury found in mom. Remember, it's a measure of mercury in blood that methyl mercury can even cross the placenta, placental barrier, and the child is exposed, the fetus is exposed.

Q In that range, how much mercury were they taking in?

A I'll do it this way if you will accept this answer. I mean, there are studies showing, for example, in a Swedish population eating four fish meals a week over an extended period of time, that would reflect a hair mercury level of around 6.6 parts

per million, 6 or more, I think it's the same thing, about 6.6. I believe it was 6.6 parts per million in that particular group. So again, and if you follow this issue at all, just the lay literature of the issue of restricting your fish intake during pregnancy, that makes sense.

Q So just to sum up then and make sure I understand it, essentially what's going on is where intake of mercury is reflected at the time in circulating blood and therefore they sample the hair close to the scalp, you can use the hair to measure what's going on in the circulating blood which you needed coming in in order for it to be reflected in the hair at all, and what these are telling you, what I'm taking for your testimony is the more you have coming in the higher it is in the hair. The less you have coming in the lower it is in the hair.

A Exactly what I would expect. Correct.

Q The third test that was mentioned by Dr. Bradstreet was the urine test for mercury, and turn to this now, turn to slide 5 that you prepared. What does the value there indicate? Dr. Staterly had done tests, and I think there is a little bit of background you need to talk about here to understand this. Was this mercury test sort of a steady state like usual?

A Sure. So let me ask you to take a quick peak at page 7 again just to remind us. We talk about an individual test, but let's look at the big picture at the same time.

Q Okay.

A That there were three different tests of mercury in the urine. The one back on page 5 is notable because this is the only test, analysis of mercury in Colten Snyder that the Petitioners claim was abnormal. So that's why I call it out on slide No. 5.

The test involves measuring mercury. This is a measure of mercury ion in the urine, and you can see down at the lower left-hand corner, which is comments that this is a postprovocative challenge, meaning that he was chelating. In all of these tests for the urine mercury analysis, the appropriate procedure would be to establish a baseline, establish a baseline in the absence of chelation. What does a chelator do? A chelator is pulling the mercury out of the kidney and it's showing up in the urine.

That's not what they did here. They didn't provide us with a baseline level of mercury, but provide a drug that we would expect to increase the mercury in the urine.

THE WITNESS: Special Master, on Monday, you asked a question about the calculation, the conversion.

THE COURT: I wasn't so far off as I thought I was.

THE WITNESS: So I provide that for you, and it's based on normalizing the 11 micrograms per gramian (ph) to the gramian (ph) levels, which are also given on the data. We have the doctor's data asterisked down on the bottom left-hand corner of the chart. It calculates out to be about 2.2 microgram per liter, which if I remember my analytical chemistry correctly, a part per million is a milligram per liter, which would make this 2.2 parts per billion.

THE COURT: And if you were converting that to parts per million?

THE WITNESS: It would be a thousandfold. It would be 2,000 -- sorry, the other direction. Move the decimal point three places to the left, so it would be .00022 parts per million.

THE COURT: Which are lower than the prechelation level in hair.

THE WITNESS: Sure. But we can't compare levels in hair to the levels in urine.

THE COURT: Understand.

THE WITNESS: Right. So having made that calculation and having described my reservation about how they went about doing this as they didn't do a before and after, if we turn to page 6, this is a table taken from a publication of Dr. Woods, James Woods. I believe it's cited as reference No. 5 in my report, and you can see just to orient you to this table, there is a measure of urinary mercury levels, urinary porphyrin levels both before and after chelation. The chelation time period here was six hours, or rather the time period before and after was around six hours.

What's important about the table is that there is a comparison between an expected occupational exposure to mercury of the dental technicians versus presumed normal members of the population, nondental personnel. If we borrow the urinary mercury levels in the nondental population, you see that it's reported to be 3 micrograms per liter.

And if we take that data and we compare it to what we find in Colten Snyder postprovocation, postchelation, it gives us a value, a comparison of 2 micrograms per liter at the time of what's being claimed to be the single test showing evidence of heightened mercury exposure with other presumably

normal people.

You can also see from this table the approach that I'm asking for, a before and an after approach, and you can also see that if we use this value of 3 micrograms per liter in the before column for nondental personnel, the normals, and we apply that to the doctor's data values on page 5, my suspicion is that the reference range used by the doctor's data is not a postprovocative challenge reference range. The value of Colten Snyder's mercury isn't really all that high after challenge. It's certainly not high if you apply the correct reference range to interpret the data.

BY MR. MATANOSKI:

Q As far as reference range, you were pointing out that you actually -- I take it that you're pointing out that if you chelate somebody, you expect to be drawing out mercury.

A Chelate someone, I expect to be drawing out metals, including mercury.

Q I'm sorry. Thank you. And it appears that --

A May I?

Q Sure.

A Expect to be drawing out metals, including

mercury independent of whether or not there is a problem with the normal excretion of mercury from the kidney.

Q Now this value then would seem actually -- again, it's not surprisingly high.

A Correct.

Q In fact, if anything, it's lower.

A I'm not impressed with that telling us there was even a single measurement showing heightened mercury in the urine.

Q Is it consistent with what we know in terms of the essentially fairly low intake of mercury by this child?

A Yes, it is. It's consistent with all of the other nine measures of mercury in hair, urine and blood, so it's not an outlier. It's not.

Q Turn to the last test that we discussed, porphyrin. In toxicology, are urinary porphyrin profiles used to measure the level of mercury?

A No, they are not.

Q Now, to prepare for a response to Dr. Bradstreet, I understand you reviewed some of the work of Dr. Woods that he had referenced. I think at the end of your report, you list the three articles of Dr. Woods that you were reading. Can you describe to me a

summary of what those articles say to you?

A Yes. Dr. Woods' research represents a work in progress. This is something that is ongoing. I know he's been at it for quite some time. At least one of these references goes back to 1991. I believe he's been working in this area prior to then. Much of his work deals with the use of urinary porphyrins and the measurement of urinary porphyrins using HPLC detection method.

The use of the measure of urinary porphyrins following prolonged high exposures to mercury in an animal model, rats, and human populations, as you saw the table that I showed, high occupational exposures. Two modifiers that are important. Long exposure, high exposures to mercury.

Q What else has the study shown us or these series of studies shown us in terms of what he's finding in his study of the population?

A Well, a few things, much of it interesting, but there appears to be a signature profile as I think you described it for porphyrins found, unique porphyrins found in urine, one of which particularly emphasizes -- there is a unique porphyrin called precoproporphyrin, and it appears that this particular porphyrin does serve as a marker of the urinary

mercury level and presumably the kidney mercury level, again under the constraints of these high, prolonged exposures, and you see that actually in the table that I borrowed to make my other point.

If we go back to page 6, then you can see that there is somewhat of a correlation between urinary mercury levels measured on the left-hand side and the urinary porphyrins measured on the right-hand side. You can see the before-and-after approach is important, before-and-after approach that he's taken, that these porphyrin measurements are responsive to chelation and that -- again, the porphyrin bodies can reflect the mercury burden in the kidney, presumably the mercury burden of the kidney because we're looking at mercury in the urine as an indication of what that burden would be. Again, high exposures, prolonged exposures.

Q So looking at the population, high exposure long term is finding a signature porphyrin profile, primarily precoproporphyrins.

A Yes.

Q And he's also noticing after chelation there seems to be a correlation of chelation drawing out some of the mercury from the kidney, it's a correlation between the levels of mercury and the

precoproporphyrins.

A Correct. So he's doing all the things that I would expect him to do to demonstrate that this is a reliable marker of mercury burden in the model systems that he's working with.

Q So essentially it becomes one of the tests then to use as a marker?

A It may.

Q Now I'm going to ask you to assume, because this is what Dr. Bradstreet did, okay, and I'm going to ask you to make the same assumptions Dr. Bradstreet, what Dr. Bradstreet assumed, that the work of Dr. Woods with respect to porphyrins is valid, okay, that there is a link between burden at least in kidney, and I have no doubt you'd restrict it to a certain population. Dr. Bradstreet applied it to Colten Snyder, so it applies to Colten Snyder. Dr. Woods' work is applicable here. It's accurate, so that we could expect that the precoproporphyrins or the porphyrin profile in Colten would behave the same way as in the population that he --

A Let me make sure I understand.

Q Okay.

A And make sure that you understand what my reservations are in answering your question.

Q All right.

A So, first of all, I don't have any issue that Dr. Woods' work is valid. I believe his work is valid. You're asking me have I seen anything in his work that says that this approach is applicable to low level mercury exposures.

Q Actually I'm not, and I'm sorry I confused you. What I want you to do is essentially step in the shoes of Dr. Bradstreet.

A Okay.

Q What I would like you to do is to essentially say, I'm going to accept that precoproporphyrins, I can look at them in Colten Snyder and figure out something about his mercury body burden, and I can make calculations or conclusions about it based on Dr. Woods' work.

Now that requires you as I understand not only to make that leap, make that assumption with respect to Dr. Woods' work as used in this case, but also it means that you're going to have to take the values that we have here as accurate.

A Right. So you're asking me to make this assumption, but also I offer that I do have reservations about the lab. I'll make the assumption, put those reservations aside.

Q The reservation about the lab.

A About the lab side. Can we learn anything from the porphyrin profiles, the three porphyrin profiles conducted on Colten Snyder?

I'm not so sure that we can if I apply Dr. Woods' findings to the porphyrin data, and the porphyrin data appears on page 8, 9 and 10 of the handout, and I believe these have been placed in chronological order beginning with the measurements that were taken on the 11th of July of 2002 on page 8. Page 9 is the 15th of September in 2006, and the last page is reported as July 26, 2007, but my understanding is the actual samples were taken in January of 2007.

So over the course of, what would that be, a year and a half, a year and a half, over the course of a year and a half, there were three samples sent to his laboratory in France to perform what appears to be a fairly specialized test. This is not something that's done in many laboratories, which perhaps explains the samples being sent to this laboratory in France.

Based on Dr. Woods' work, in the precoproporphyrin measurements over time, what he showed was you take his animal studies -- again, the

rats were exposed typically to 10 parts per million methyl mercury for six weeks if I'm remembering correctly his 1991 paper that I cited -- exposed for a long period of time to these high levels of methyl mercury, and then the exposure was stopped. Then the urine samples were collected and the porphyrin values, the porphyrins were measured.

Over time, you would expect based on his research that the porphyrin values would decrease, particularly for the signature porphyrin, precoproporphyrin. I mentioned a signature porphyrin a couple of times here, at least I think I did, the signature precoproporphyrin. You will notice on each of these tests, the three dates that I am referring to, is that not only does the signature porphyrin change, but all of the porphyrins were changing, so in the data, I'm not seeing the signature. That's one issue.

The other issue is that over the course of time, I'm not seeing the porphyrin lines change. Now remember, the exposure to mercury occurred eight years ago, so I'm surprised, and what's most surprising, and again, this is in comparison to the table that I showed you from Dr. Woods' publication, that Colten Snyder was chelated during this period of time, and

you would expect the chelation will be changing his porphyrin lines, and they are not changing. And so it again makes me suspicious that these data are true and a representative indication of the mercury burden in this individual or that this approach can be used as a reliable indicator of that mercury burden, and I emphasize reliable indicator because I have to step in Dr. Bradstreet's shoes. That's what he said.

Q So in other words, if you were to assume, make an assumption that Dr. Woods' work can be applied here, you assume this lab, this is not following the pattern that should be followed based on Dr. Woods' tests?

A Correct. And the reason why I think it's not fitting the pattern is because it's not a valid assumption, that it can be applied to a low level exposure.

Q The other reservation that you have too, you have another reservation with respect to the actual values from the lab.

A Yes. I had some reservations about some issues with the lab, that's correct.

MR. MATANOSKI: I have nothing further at this time.

THE COURT: Break before we do the cross-

examination?

MR. POWERS: You said it first. I was going to ask. Yes, please. Thank you.

THE COURT: How about we reconvene just shortly after 4 or 5 after 4?

(Whereupon, a short recess was taken.)

THE COURT: We're back on the record in the Snyder case. Dr. McCabe is on the witness stand, and you may cross-examine, Mr. Powers.

MR. POWERS: Thank you, Special Master.

CROSS-EXAMINATION

BY MR. POWERS:

Q Good afternoon, Dr. McCabe. Thanks for being here. My name is Tom Powers. I'm one of the lawyers that represents the Snyder family, and I'm also one of the attorneys on behalf of the Petitioners Steering Committee, and you understand that some of the testimony here is being applied to cases in general that are pending in the autism proceeding, is that correct?

A Yes, I do understand that.

Am I close enough to the microphone?

Q You are absolutely close enough to the microphone.

A Good.

Q I'm assuming I am too.

A Yes, you are.

Q All right. Now have you been here in the room for testimony throughout this proceeding beginning Monday morning?

A Yes, for most of it.

Q For most of it. Were you here during the testimony -- well, it might be easiest. What testimony did you miss?

A I missed portions of this morning's testimony.

Q Okay. Any other days?

A No.

Q And in preparation to come and testify here today, it certainly sounds like you reviewed the record that was developed in the Cedillo case?

A Yes, I did.

Q And in particular, you reviewed the testimony of Dr. Byers, is that right?

A That's correct.

Q The testimony of Dr. Aposhian?

A That's correct.

Q The expert reports of those two folks?

A I don't recall that I reviewed the expert reports. I don't recall that I reviewed those. I may

have. The safe answer is I think not.

Q Okay. And in all seriousness, if you don't know something, I'm comfortable with the answer that you don't know. I certainly don't want you to be speculating or guessing here.

A Sure. I understand.

Q Now you've also cited some literature, I think it's five citations in your expert report, and you discussed all the work in your CV. Aside from the Cedillo materials that you described, the literature that you specifically cite here and generally the literature that's available to you in your area of expertise, anything else that you were examining in order to prepare for your testimony?

A I think nothing especially since you gave me the umbrella term of the literature that's available. So yes, I can do a PubMed search and find many papers. Nothing specialized for that.

Q Okay. Great. Now I have a question about this immune dysregulation issue. At what level of mercury exposure would you expect to see some form of immune dysregulation?

A Ask me the question again, please.

Q Sure. At what level of mercury exposure might you expect to see some form of immune

dysregulation? And this is in humans. We're not talking about in-vitro, animal models. Specifically humans.

A It's a difficult question to answer and I'm not hedging in my answer. There is literature looking at exposure, chiefly in occupational exposures. I'm thinking of papers with, for example, the urine mercury level. Remember these would be in occupational exposure, so you would expect in the target populations quite high levels, and those are around 50 microgram per liter mercury present in the urine.

And the studies are not very sophisticated, which is why I stay away from those types of approaches, because you can't ask as interesting questions. The studies are not very sophisticated in that the approaches to, well, count subtypes of lymphocytes, subtypes of T-cells or B-cells and K-cells.

Q And you correlate those counts through --

A Correlate those changed -- correct, you correlate the changes in counts to the mercury exposure level.

Now you asked me how much mercury would you need to be exposed to. I can't speak to that based on

the literature. I can speak to in those types of reports what are the reported urine mercury values, for example. I can tell you that in over half a dozen papers that come to mind in the unsophisticated approach that's taken that the data are all over the place. Some of them show increases in T-cell numbers, decreases in T-cell numbers. It's not a very sophisticated approach as I've told you because it doesn't say anything about the functionality of those cells.

If I use a model that I discussed earlier, it's essentially an A and B approach, connect A to B, and it's limited in that it's difficult to take a view of that. You can speculate what it might be. It's difficult to put that speculation into a cogent argument here because the values in individual papers vary.

Q Do you have a sense then of what the range of values are across some of those individual papers? I mean, you used an example of 50 micrograms per liter for urine samples, and that's 50 micrograms of mercury in the urine, correct?

A Correct. Correct.

Q That's one number. Do you have a sense in the published literature that you're familiar with

what range of urine mercury would you expect to see in an immune dysregulation response?

A I don't know that that literature supports that it's an immune dysregulation, so I am not willing to say that a change in lymphocyte numbers is equivalent to an immune dysregulation. The immune system is more complicated than that. You can't simply count the cells, so that's a caveat to the answer I'm giving.

From the literature, these are papers that have been in the literature for quite some time. I haven't reviewed the details of many of those papers, of all of these papers recently. I don't know what the range would be. I would not be surprised that many of them -- two come to mind, 150 microgram per deciliter, another in the 40s.

Q The 40s. You also mentioned that one of the limitations of these studies is they generally do little more than count cells.

A Correct.

Q Are you familiar with any studies that examine mercury exposure and immune regulation or immune response that do more than count cells?

A In humans?

Q Yes. And if so, at what sort of levels

would you expect to see a response based on exposure?

A Nothing that's coming to mind right now. Nothing that's coming to mind right now.

Q I want to shift gears a little bit and talk about immune issues and talk a little bit about some of the mercury issues that relate to these various tests. I noticed in your expert report, you mentioned that Dr. Woods' work shows that heightened urine porphyrins may be a marker following exposure to high level, prolonged exposure to high levels of methyl mercury.

A That's correct.

Q Are you aware of publications, including publications perhaps by Dr. Woods, of other forms of mercury other than methyl?

A Yes, and I would expect based on how I know that mercury is handled that other forms of mercury showing up in the kidney as the mercury ion would respond, would show altered profiles. In my expert report, I am referring to his animal studies with the rats where he had exposed the rats for a long period of time, as I indicated on direct.

Q Yes, and that's just what I wanted to clarify because it gave me the impression when I read it that you were excluding other forms of mercury, but

in fact that is not the case.

A You are correct. In the application of Dr. Woods' research to the matters before this Court and this case, the issue of speciation of mercury is not an issue that I meant to make, but the issues of a lot of exposure and high exposure I think remain.

Q Yes. Yes, and the specie issue you talk about a little bit also. It is something that we should at least touch on. In fact, let's start talking about it now a little bit, the different forms of mercury.

Now my understanding is that when Thimerosal is injected into somebody, Thimerosal, one of the breakdown products is ethyl mercury, correct?

A That's correct.

Q And ethyl mercury is an organic form of mercury.

A That's correct.

Q And peer-reviewed published literature over the last couple of years indicates that ethyl mercury has a greater likelihood of being deposited in the brain than does methyl mercury. That's the Burbacher study, is that correct?

A I have seen the Burbacher study. I have not looked at it more recently. My understanding aside

from the Burbacher study is that you are correct in that Thimerosal is broken down into ethyl mercury. Ethyl mercury, the comparisons are always made between the toxic kinetics, the movement of mercury in different tissues of the body, the comparisons are often made between ethyl mercury and methyl mercury. Ethyl mercury is broken down into mercury plus 2 more quickly than methyl mercury.

So ask me your question again just so I make sure I don't go off on a tangent here that's irrelevant to answer your question.

Q The question was, and I appreciate your getting to the speciation of the Hg+2 because that Hg+2 that ethyl mercury tends to break down into in the body, as Dr. Burbacher points out, tends to be deposited in the brain, not in the form of ethyl mercury but in the form of an inner --

A Well, it wouldn't get into the brain as mercury plus 2.

Q But once in the brain, it would be --

A Once in the brain, as in all tissues of the body, ethyl mercury would break down more rapidly into mercury plus 2, and mercury plus 2 being the ultimate toxic species of mercury as most metal toxicologists believe.

More methyl mercury gets into the brain than ethyl mercury. Since ethyl mercury breaks down more quickly, if you compare the total mercury level between methyl mercury and ethyl mercury, you will find more methyl mercury, more total mercury in the brain in the case of methyl mercury. You will find equivalent levels of mercury plus 2 because the ethyl mercury that gets into the brain is broken down to mercury plus 2 more rapidly.

Q And then the mercury plus 2 that's in the brain, that's mercury at that point behind the blood-brain barrier.

A Correct.

Q So that's mercury that is not going to be excreted through the hair, for example, correct?

A You would not expect that to be readily exchangeable and appear back in the blood and be detected in hair as a measure of the mercury that was found in blood.

Q Okay.

A Correct.

Q I think I follow that.

A You're asking me about the excretion of mercury at the hair, and I'm telling you that the measure of mercury in hair is a proxy for the mercury

that's in the blood.

Q And that's the exact term you used in --

A It's a proxy for the organic mercury that's present, because remember it's not going to be in the hair unless it's in the organic form.

Q And that's what I was trying to get at. And I will try to ask direct questions only because we can make this a lot quicker. My only question was the Hg+2 that's in the brain, the presence of that form of mercury in the brain will not be detected on hair tests, correct?

A That's correct.

Q It will not be detected in urine tests, correct?

A That's correct.

Q It would not be detected in blood tests, correct?

A That's correct.

Q It wouldn't be in any other excretory pathways where one might expect to find mercury, feces, fingernails, that sort of thing. You just wouldn't see it being excreted.

A That's correct.

Q Okay. And we know that the mercury, Hg+2 that's in the brain, deposited in there according to

Burbacher has an indeterminant efflux, isn't that right?

A Correct.

Q So none of the testing that you've discussed today, the blood tests, the urine test, all the work that Jeff Bradstreet was doing, none of these tests would be informative about the presence of Hg+2 in Colten Snyder at any point in his life because this is all based on excretion.

A If I may, and if I am spiraling away from answer your question, you certainly will stop me. You're making the assumption that there is a particular affinity for Thimerosal going to the brain and not in any of these other tissues where it would be metabolized, so it would be metabolized and would then be readily measurable, for example, in the kidney or in the urine.

Q Oh, yes. That was the point.

A I just want to make sure that in my answering these questions right that there is no way of assessing because it all went to the brain, and there is no measure, and there is no noninvasive measure to detect the mercury that's in the brain, that we don't have any way of evaluating the exposure of mercury that occurred.

Q Yes, and that's my point. My question was not about the exposure to mercury that occurred.

A Okay.

Q My question specifically was mercury in the brain, Hg+2, we wouldn't find it anywhere in the tests here. You wouldn't expect to.

A That's correct.

Q Now the porphyrins as I understand, porphyrins are an intermediate byproduct of hemosynthesis? Is that a correct understanding?

A That's my understanding as well.

Q Hemosynthesis is something that happens in every cell?

A Yes.

Q And that would include cells in the brain?

A Yes.

Q And hemosynthesis is a biosynthetic process, I guess a many step process where you take some raw material and through this process you build hemo, hemo is the end product of the hemosynthesis, is that right?

A That's correct.

Q The idea with the porphyrins is that at certain stages of that process of the various of the steps, the body naturally makes excess porphyrin as an

intermediary byproduct, right?

A Correct.

Q And that excess then gets excreted and you can measure it in the urine, right?

A According to Dr. Woods' work, yes, you can. Yes, yes, you can.

Q Right.

A Not just his work. Yes.

Q I'm not talking about signature stuff yet. I'll get there.

A Yes, you can measure porphyrins in urine.

Q Exactly. And the hypothesis, the working hypothesis of Dr. Woods' work since he first published back in 1977 has been that mercury has a unique impact at certain specific points of the hemosynthesis cycle, correct?

A That's my understanding. That's correct.

Q And by being porphyrinogenic, it changes the typically excretory profile of the porphyrins that are being thrown off by this synthetic cycle, correct?

A Correct.

Q And so Dr. Woods has posited that if you can then analyze the porphyrin levels of somebody who has been exposed to mercury and somebody who is not exposed, you'll see a different expression in the

ratio of the various porphyrins. You have an expectation for an unexposed population based on what we know about the natural excess. You would then see -- this is why it's a signature -- that the mercury gets into some of those steps and disrupts the ratio of porphyrin that are released, correct?

A That's my understanding. That's correct.

Q And that's measurable.

A Keeping in mind that the porphyrin profile that's present in urine can also be modulated by other metals and by other toxic agents.

Q Oh, absolutely. Absolutely. I think that's really the body of this work that's very clear, that in fact his mercury model actually follows upon a lead model, and so we're sort of learning what we learn about lead, we then learn things about mercury, and this is a way to do it because this is urine testing.

A Absolutely correct.

Q And Dr. Woods has also published work indicating and associating various levels of porphyrinia with some behavioral -- this is some of the dental studies. Are you familiar with those?

MR. MATANOSKI: I'm going to object to going into that just because we certainly haven't been going into that on direct.

THE COURT: Well, it's part of his report. The articles that he cited in his report cover those.

MR. MATANOSKI: Oh, I'm sorry. Those are the ones that he --

THE COURT: There were articles attached to his report. I think they are fair game.

MR. MATANOSKI: Oh, absolutely, absolutely. I didn't know that you were going into the articles.

BY MR. POWERS:

Q So the question was are you familiar with the literature of Dr. Woods that looks to associate porphyrinia that he claims is significant for mercury exposure to behavioral in dental workers? Are you familiar with those?

A Yes, I'm familiar with it. I'll tell you as an immunotoxicologist with expertise also in metal toxicology, the aspects of those papers that dealt with the neuro outcomes I don't remember. That's not my area that I was interested in those particular papers.

Q So you were interested in the toxicology aspect and not the neurological outcome aspects?

A I wouldn't say I was completely disinterested. I'm telling you that if you're going to ask me questions about the neurological outcomes in

those papers, I don't remember.

Q I was just asking --

A So the answer is yes, I'm aware that he's made and he's attempting to make connections between the mercury exposure, the porphyrin profiles and the neuro behavior outcome as is being done in this case, the same.

Q On your slide No. 4, this is out of the blue, but I'm wondering -- this is a math question.

A And it's asking me for a password here. Oh, I see.

Q I don't think we need the slide. It's slide 4.

A Yes.

Q The hair mercury levels are being measured in parts per million.

A Yes.

Q Is there any way to extrapolate from parts per million of mercury in a hair sample into micrograms per kilogram of body weight assuming you knew how much a subject weighed?

A You would extrapolate these data to micrograms per gram of hair. I believe you would measure the hair.

Q But you would be able to make an

extrapolation to body weight?

A You would be able to do that once you knew what the body weight of the subject was and the weight of the hair. I think you could make that kind of a thing.

Q And it's not just an abstract question I asked because so often in the literature relating to Thimerosal and mercury that is the unit of measure. It's micrograms of the target per kilogram of body weight.

A Correct.

Q I'm not going to ask you to do any conversions, but if you think that it's possible to do that, that's informative for me down the road.

A Yes, and I see that in the literature as well.

Q Okay. Now the various tests that Dr. Bradstreet performed that you were discussing, these tests all were two years later from the date of Colten Snyder's last known Thimerosal exposure, is that correct?

A I believe that is correct. Yes, that's correct.

Q So none of the data that's presented in any of these tables is informative as to Colten Snyder's

body the day that he received the MMR vaccine back in 1998, is that correct?

A That's correct. I think I made that point.

Q One wouldn't expect to find it.

A That's correct.

MR. POWERS: I have nothing further.

THE COURT: Okay. Just to follow up on that, if I inject a set amount of ethyl mercury in the form of Thimerosal into a 11 kilo baby, and let's assume none of it's excreted, it's going to be a different burden than when that child weighs 50 pounds, a different percentage of his body weight.

THE WITNESS: Correct.

THE COURT: So what he got when he was two months, four months, six months doesn't really translate into what you would expect to see in terms of urine level, hair level or blood level here?

THE WITNESS: Sure, sure. That's correct, it doesn't. Right. I think the answer is yes.

THE COURT: All right.

THE WITNESS: So the issue is that I don't see any evidence of high mercury burden.

THE COURT: Now let's talk about mercury levels. You indicated, and I am aware that you cannot translate urine levels into hair levels or blood

levels, but is there a conversion measure that is used, that is, blood mercury levels are generally so many times greater than urine levels? That's a question.

THE WITNESS: That's a question. Certainly there are conversion factors for blood levels of mercury and levels you would find in hair.

THE COURT: And it's roughly equal.

THE WITNESS: It's roughly around 1 to 250.

THE COURT: Okay.

THE WITNESS: Most of the mercury that's in the blood is associated with the red blood cells. It makes the plasma that's important because the plasma fraction is the fraction that's readily exchangeable in tissues. The plasma conversion to hair is around 1 to 2,500.

THE COURT: But you're not familiar off the top of your head with any conversion of blood level to urine level?

THE WITNESS: Off the top of my head, no, I am not.

THE COURT: Okay. That's fine.

THE WITNESS: The conversion factor for hair to blood I see in a number of the literature that I'm reading, so I don't know. I'm not aware of it off the

top of my head, and I don't know of one available.

And why would that be just if I may? Why might that be and why would it make sense is that as the kidney being the ultimate organ that mercury plus 2 is going to, right, it's going to move from the kidney into the urine.

THE COURT: Okay. And ethyl mercury has more of an affinity for the kidney, is that correct?

THE WITNESS: I don't know that.

THE COURT: Okay.

THE WITNESS: I don't know if that's correct.

THE COURT: Okay. How do the methyl and ethyl mercury half-lives or half-times in the body compare?

THE WITNESS: The half-times?

THE COURT: That is, if I inject the same amount of ethyl mercury versus methyl mercury, ethyl mercury into one individual, methyl mercury into another individual or group of individuals, looking at excretion patterns.

THE WITNESS: Yes. I'm thinking of two pieces of information that come to mind, and it's not a side-by-side type study in answering your question.

THE COURT: I understand, but we usually

don't inject either into people deliberately anyway.

THE WITNESS: Oh, injection of methyl mercury versus exposure.

THE COURT: Yes. I'm looking at similar modes, so whether we use ingestion, whether we use subcutaneous injection, and does it differ between those two.

THE WITNESS: So that I also have to offer the two studies that I'm thinking about. So methyl mercury, I have in my head that the half-life of methyl mercury is about 65 days. That's my recollection. The half-life of methyl mercury is about 65 days. The half-life of Thimerosal is more on the order of a week or two as I recall.

THE COURT: All right. You indicated some degree of familiarity, am I correct, with the French laboratory to which the --

THE WITNESS: Familiarity, I don't know. I indicated that I had some reservations about the data obtained from that lab.

THE COURT: Okay.

THE WITNESS: I don't have any familiarity with the lab.

THE COURT: Okay. Is that reservation about this particular data or data in general from that lab?

THE WITNESS: Oh, this particular data.

THE COURT: And it's because this data is somewhat anomalous in what you would expect in terms of a chelated profile show?

THE WITNESS: Well, that's the start.

THE COURT: Okay. Where do you go from there?

THE WITNESS: The start is being asked to make an assumption that I can apply Dr. Woods' work to a lower level of exposure.

THE COURT: Okay.

THE WITNESS: The assumption that the data are valid if they don't fit the signature profile, as I indicated. So the reservations that I have, if we turn to page, I think it's page 10, page 10.

THE COURT: And that would be of Trial Exhibit 3.

(The document referred to was marked for identification as Respondent's Trial Exhibit 3.)

THE WITNESS: This would be -- yes, and it's the urinary porphyrin profile as measured or submitted for measuring on July 26, 2007, and my comments I think can be applied to the other two tests as well.

I'm bothered by the column dealing with interpretation, and you'll see that in each case it says for the urine porphyrin on the right-hand side.

THE COURT: Yes.

THE WITNESS: The average rate, the next one down, increased rate, slightly increased rate all the way down. In each case, the word "rate" is used. So this is a laboratory that's interpreting their data and they are offering an interpretation involving rate.

Now everyone that drives a car knows that rate is a measure per unit time, and this is a single point in time measuring these porphyrin levels, and so I don't know what to make of their interpretation and so it's a flag. Am I wrong about that? I don't know. It's a flag that the interpretation is using. It's a flag to me -- again, this is an exercise in math -- how do we go from nanomils of particular porphyrin per gram of creatinine -- sorry, I'm going to do it the other way. How do we go from first nanomils --

THE COURT: Per liter.

THE WITNESS: -- of a porphyrin per liter to nanomils per gram of creatinine, and that requires the normal answer, urinary creatinine is found down at the bottom, in this case 548 milligrams per liter.

If I applied that normalizer to each of the values in column 1, for at least the first two, and I don't have this -- the first two, the calculation is different than what's reported here. Is it wildly off? No. But if they can't perform a simple math conversion in reporting a value, and I'm suspecting -- if I'm wondering if the data fit the diagnosis, I'm left with trying to figure out, well, what's the skew here.

I think the last thing to draw out is that the creatinine levels, and so here is where you have to go from page 10 back to page 9, the normalizer changes. The urinary creatinine level changes. So can urinary creatinine values change from 924 to 548 over a five-month period? Possibly. The 924 milligrams per liter, this is on page 9.

THE COURT: Right.

THE WITNESS: The 924 milligram per liter creatinine value, doctor's data, there is a value for creatinine taken 10 days earlier that differs by hundreds.

THE COURT: It's 20.3.

THE WITNESS: It's 20.3. So if you make the conversion, it becomes 203 grams per liter. Exactly. It's over a 10-day period the creatinine value changes

from 200 to 900. This is a specialized test that's being sent to a lab in France, and my reservation is, again I may be wrong, but it raises a flag for me. It's not that they are incapable or if they reported suspect creatinine values, which is something anybody can measure, what does that do to the values of the rest of the data?

The last issue to draw out, and again it's in comparison between porphyrin profile in one, two and three, so pages 8, 9 and 10, is that the reference values change between tests. Now can reference values change within a laboratory? Sure they can, and I expect they could. But what's the explanation for this change in reference values? It's not provided.

The larger issue here is that this is a specialized test. We wouldn't do this test or have access to do this test at the University of Rochester or the medical centers around the United States presumably. That's why the samples are being sent to France.

THE COURT: So you're saying this kind of testing is not being done in the United States?

THE WITNESS: Correct.

THE COURT: It's not being done by Dr. Woods?

THE WITNESS: Well, that would be a question. If I got turned onto the idea that urinary porphyrin profiles will be the new way to assess mercury in the urine, it seems to me that I would start a conversation with Dr. Woods and find out what's the protocol that I should be following to do this.

Remember the protocol itself would involve again the before-and-after approach that he reported in the table, and I showed you before-and-after chelation. It would involve an approach where I am measuring the urinary mercury levels in concert with measuring the urinary porphyrin levels, right, because after all I'm interested in showing that there is a connection, and that's not being done here.

So it's a specialized test perhaps at the front end of this. The reason that it's not done in other labs is because we wouldn't know what to do with the data. We don't know what the reference values should be. So here I don't think they know what the reference values should be either. They simply change. Am I wrong? I may be, but again, these are the issues that raise flags in the application of this porphyrin approach to the question of is there significant kidney burden of mercury here.

THE COURT: Okay. It appears that these tests, it looks to me, are being done for the purpose of demonstrating that there is a body burden of mercury that is not being detected on blood or urine tests. Is that how you interpret it?

THE WITNESS: I interpret that that's what their intent is, to have an alternative way of measuring the kidney burden of mercury because the direct measure of mercury in urine shows --

THE COURT: Very low.

THE WITNESS: -- very low, but again, the problem there again was by the approach. Remember there wasn't a before or after chelation, very limited. If I was allowed to design this as a research study, I would rather they go back and do the pre- and postchelation and measure mercury in the urine, directly measure mercury in the urine. Show me that it doesn't respond to chelation.

Well, I guess show me that it does respond to chelation, and then you would need a new test, a new test of porphyrin values to give me an indication of what the kidney mercury value was. I'm speaking to the efflux issue.

THE COURT: Okay. And on the mercury efflux disease, in your opinion, is there evidence that

individuals do have a mercury efflux disease analogous to Wilson's disease for copper? Do you have an opinion?

THE WITNESS: I don't have an opinion.

THE COURT: Okay.

THE WITNESS: You're stretching my --

THE COURT: All right. Fair enough.

Let's back up then and talk about one of the articles you submitted along with your report, and I'm referring to the -- let's see if I can find which one it is -- the Heyer, H-E-Y-E-R, article. I'll give you a copy of it if necessary.

THE WITNESS: Yes, if I could get a copy. Do you know who the senior author is?

THE COURT: He is the primary author. Woods is also on the article.

THE WITNESS: Okay.

THE COURT: It's tab 5 to your exhibit.

THE WITNESS: Okay. This is the journal.

THE COURT: And it's the cascade analysis of the interaction of mercury and porphyrin oxidase polymorphous.

THE WITNESS: Polymorphism study, yes.

THE COURT: Okay. How do you interpret that article with regard to whether individuals excrete

mercury in different ways depending on their -- this polymorphous? And then I'm going to ask you to interpret if you have something to say, to interpret that with regard to this porphyrin profile?

THE WITNESS: May I have a peak at the page?

THE COURT: I'm sorry?

THE WITNESS: May I have a peak at the page?

THE COURT: You may. Here. I'm going to hand the paper over, and it's tab 5.

(Pause.)

THE WITNESS: And you're asking me?

THE COURT: This article seems to indicate that there is a pattern of dose and time-related porphyrins predictable among most human subjects occupationally exposed to mercury, but about 15 percent of subjects from several studies display an atypical response characterized by excretion of substantially higher concentrations of three particular porphyrins.

THE WITNESS: That's my understanding as well.

THE COURT: Okay. And then so that these are individuals that excrete mercury differently. Is that too much of a jump?

THE WITNESS: I'm trying to find where in

the paper an association is made between the mercury excretion and the porphyrin.

THE COURT: I think that's what they are looking at. They tried to associate the porphyrin excretion patterns with those individuals who had the CPOX-4 polymorphism.

THE WITNESS: I think I understood it this way.

THE COURT: Okay.

THE WITNESS: Here is what I take from this paper, and I think it essentially states there is some percentage of the population, 13 percent, that has a polymorphism in the gene that's responsible for converting the porphyrins to signature porphyrin.

THE COURT: Okay.

THE WITNESS: And therefore in those individuals, you see a heightened peak in that particular report.

THE COURT: And that heightened peak would be in 7CP?

THE WITNESS: Is it in the KICP?

THE COURT: And the KICP.

THE WITNESS: Right. So that tells you that they have a special sensitivity of that enzyme to mercury.

THE COURT: Okay.

THE WITNESS: That's what it told me.

THE COURT: All right.

THE WITNESS: That's interesting. Why is that interesting in general is because of the issues of gene environment interactions.

THE COURT: Exactly.

THE WITNESS: Right.

THE COURT: And essentially what we have heard, if you read Dr. Aposhian's testimony, he testified that some people excrete mercury differently than others, than a small percentage of population. Now he referred to the pink disease and the 1 in 500 figure --

THE WITNESS: Yes.

THE COURT: -- that came from someone whose cited article didn't say that at all, but that 1 in 500 figure has been repeated throughout the literature we've been supplied.

If there is, as this higher study indicated, some association with that polymorphism and urinary porphyrins as measured, how do those measurements for those individuals compare -- I mean, is that why Colten's results are odd? That's what I'm asking.

THE WITNESS: Well, we don't know, for

example, which CPOX polymorphism is, so I can't speculate.

THE COURT: Well, let's not speculate about whether he has it or not, but are his results consistent with what Heyer found? Heyer or Heyer, however you want to pronounce it.

THE WITNESS: Not as I recall what Heyer is showing here. Now, I mean, Heyer is showing a refinement --

THE COURT: On Woods' work?

THE WITNESS: -- of Woods' work, and Woods is on this, but Heyer is showing a refinement of what this lab has been studying, right, and the refinement goes to the enzyme. Polymorphism in the gene that goes to the enzyme, right, that's responsible for producing this signature. It doesn't speak to the mercury efflux issue and the potential for polymorphism in other genes that are responsible for the mercury efflux.

THE COURT: Okay. I understand that I may be doing apples and oranges, so let's take the mercury efflux out of the situation.

THE WITNESS: Okay.

THE COURT: Given this article's work on this polymorphism and how it affects the excretion

levels of the porphyrins, what I'm asking is are Colten's excretion levels as reported here, and I realize they are on several different levels here in your charts 8, 9 and 10 on Respondent's Exhibit 3, consistent with the unusual excretion, porphyrin excretion pattern that Heyer observed or not?

THE WITNESS: Okay. I think no.

THE COURT: Okay. Thank you.

THE WITNESS: I can provide an explanation.

THE COURT: Sure.

THE WITNESS: I think the answer is no, and Heyer's work still goes to a lot of high exposures.

THE COURT: Okay.

THE WITNESS: It's the application of prolonged high exposure to a genetic polymorphism in CPOX-4.

THE COURT: All right.

THE WITNESS: So it doesn't help in explaining Colten Snyder's profile.

THE COURT: And Colten Snyder's profile does not look like those with high exposure and CPOX-4.

THE WITNESS: As I testified, I don't see that Colten Snyder's porphyrin profiles are acting as the bulk of Dr. Woods' research has said that they should.

THE COURT: And that's how I read your report, but it didn't specifically address this issue.

THE WITNESS: Yes.

THE COURT: Those are all the questions I have. Any followup? Go ahead. No, Mr. Matanoski, you get to go first. That's just the way it works.

REDIRECT EXAMINATION

BY MR. MATANOSKI:

Q Mr. Powers asked you about some studies with respect to some values you found -- at the very beginning of your cross-examination, studies were conducted where there may be some in humans, and there may be some unusual and a difference in you said the cell count.

A Yes.

Q In those studies, now only if you recall, were the individuals in those studies medically immunosuppressed or clinically immunosuppressed?

A That's the point. Those types of features, those types of issues were not addressed in those studies from my recollection. It was again another A and B connection, BB and lymphocyte numbers and comparing the mercury exposure as indicated in the urine.

Q They never got to the result we're

interested in about --

A Well, not that I recall, but the immunotox literature, the metal tox literature, there are studies that have examined frequency of colds, the number of sick days, things of that nature. My recollection of that work applies more to the lead literature than the mercury literature. But in the specific studies that I'm thinking about where there were attempts to make correlations between lymphocyte number and urine mercury, I don't recall, but I don't think that other evidence of immunosuppression such as frequency of infections was examined.

MR. MATANOSKI: Thank you.

THE COURT: Go ahead, Mr. Powers.

MR. POWERS: Thank you.

RECROSS-EXAMINATION

BY MR. POWERS:

Q Just a couple of quick things. On slide No. 10, you were talking about the term "rate" there.

A Yes.

Q Is there any possibility that what is meant to be stated there is "ratio" and perhaps it's a language issue? I noticed some other sort of grammar and semantic errors in there. Would ratio be an appropriate term to use where rate is not?

A It would not be. I thought about our good friends in France and whether that would be indicated in the report. Ratio is not the issue, and it's not in my slides, but you know that each one of these porphyrin profiles contain additional pages where the ratios were calculated, and actually part of it's here below and you can see ratio, they are using the word "ratio" just fine. So no, I don't think it's ratio instead of rate.

Q Would that be an appropriate term to use given Dr. Woods' work looking at to some extent at least the relative ratio of the various porphyrins that are displayed?

A I understand that, and again, I'm going to say no, and I don't think so because it's not the interpretation in terms of average rate. The issue of rate refers to each one of these rows that are not providing the ratio. The ratio is provided elsewhere in the report.

Q Okay. A moment ago, actually early on in some questions the Special Master was asking, you said there was no evidence of heightened mercury levels in Colten. I did have a question on porphyrins.

Now hemosynthesis is happening in cells in the brain. We are talking about that. So there would

be porphyrins even as to porphyrinia, even with a typical porphyrin excretion pattern, the hemo process in brain cells would be generating porphyrins, correct?

A Yes.

Q Do those porphyrins cross the blood-brain barrier and end up in urine? Do you know?

A I believe it depends on whether they are oxidized or reduced, whether we're talking about porphyrins or porphyrinogens, but again --

Q I'm talking about the porphyrins that would be a byproduct of a typical hemo cycle where they are overcreated at certain steps.

A Yes. Yes. I don't know. I don't know.

MR. POWERS: Nothing further.

(Witness excused.)

THE COURT: All right. We are finished for the day and almost on time. We will reconvene at 9:00 tomorrow morning.

(Whereupon, at 4:55 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 9:00 a.m. on Thursday, November 8, 2008.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 01-162V

CASE TITLE: Colten Snyder by and through Katherine Snyder and Joseph Snyder, his natural guardians vs. Secretary of Health and Human Services

HEARING DATE: November 7, 2007

LOCATION: Orlando, Florida

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 Department of Health and Human Services.

Date: November 7, 2007

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