UNITED STATES
COURT OF FEDERAL CLAIMS

IN RE: CLAIMS FOR VACCINE INJURIES RESULTING IN AUTISM SPECTRUM DISORDER, OR A SIMILAR NEURODEVELOPMENTAL DISORDER,	)	
FRED AND MYLINDA KING, PARENTS OF JORDAN KING, A MINOR, Petitioners,	)	
v.	)	Docket No.: 03-584V
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	)	
GEORGE AND VICTORIA MEAD, PARENTS OF WILLIAM P. MEAD, A MINOR, Petitioners,	)	
v.	)	Docket No.: 03-215V
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	)	

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Courtroom 402
National Courts Building
717 Madison Place NW
Washington, D.C.
Monday,
May 19, 2008

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

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

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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
4	1780	--	J. Brent slide presentation
5	1974	--	R. Mailman slide presentation

P R O C E E D I N G S

(9:00 a.m.)

SPECIAL MASTER VOWELL: We're on the record in the omnibus autism Theory II hearing in the Mead and King cases, and Respondent, I believe you're about to begin presenting your case?

SPECIAL MASTER HASTINGS: Let's go off the record for a minute.

(Whereupon, a short recess was taken.)

(The document referred to was marked for identification as Respondent's Trial Exhibit No. 4.)

SPECIAL MASTER VOWELL: All right. We're back, and I think we have our technical difficulties resolved. Dr. Brent is on the witness stand. If you would raise your right hand, Dr. Brent?

Whereupon,

JEFFREY BRENT, M.D.

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

SPECIAL MASTER VOWELL: Thank you. You may proceed, Respondent.

MS. RENZI: Good morning, Special Masters.

//

DIRECT EXAMINATION

BY MS. RENZI:

Q Good morning, Dr. Brent.

A Good morning, Ms. Renzi. Good morning, Special Masters.

Q You've already stated your name for the Court. Could you please give us your title?

A My title?

Q Your professional title.

A My professional title? I am --

SPECIAL MASTER VOWELL: I want to make sure that Dr. Brent's mic is working. Can you check that? That mic, Dr. Brent, is simply the one that the Court reporter is using. There should be another one. There it is.

THE WITNESS: Okay. I'm talking into the wrong one. I am a Clinical Professor of Pediatrics and Medicine at the University of Colorado Health Sciences Center. I'm a medical toxicologist. I'm also in private practice.

BY MS. RENZI:

Q And could you briefly describe your educational background and training?

A Sure. Where do you want me to start? How far back?

Q Start with your BA.

A My BA?

Q Yes.

A Okay. I'm originally from New York City. If you've listened to me long enough, you've probably realized that by now, and I got my BA degree at Hunter College in chemistry. I subsequently got a masters degree in molecular biology and a PhD in biochemistry from Mount Sinai School of Medicine after which I went to medical school at the State University of New York at Buffalo. Upon graduating from medical school, I went to Boston to Harvard where I served as an intern and junior resident in general surgery.

After that I did a couple of other things and ultimately completed my primary residency in emergency medicine at Emory University School of Medicine in Atlanta. Following completion of my primary residency, I moved to Colorado to do a two-year fellowship, subspecialty fellowship in medical toxicology at the University of Colorado Health Sciences Center and did that fellowship, completed that fellowship, became subspecialty board certified in medical toxicology.

I got invited to stay on the faculty of the university and have remained on the faculty ever

since, rising from assistant to association to full professor, which is the highest achievable rank in our institution.

Q And could you just briefly describe some of the honors you've recently received?

A Well, sure. I guess if I had to pick one recent one that really stands out quite a bit it would be my so-called Louis Roche Award. This is an award given to one person every year by the European Association of Poison Control Centers and Clinical Toxicologists, and it is given to that individual, most often Europeans, who has been felt to have contributed greatly to the field over some period of time, and I was recently given the Louis Roche Award by that organization.

There have been others, but I think that's probably the most meaningful recent one to me.

Q And do you consult with any federal agencies?

A Yes, I do.

Q Could you describe some of your duties there?

A Sure. I have on and off consulted with various federal agencies including the Department of Justice, not necessarily related to these issues, but

we had in Colorado a Mountain States Drug Task Force dealing with sort of the war on drugs, and I was consultant to them about drug paraphernalia and how people use drugs and what various things that they encounter over the course of their activities, mean and how various pieces of apparatus and paraphernalia are used.

I have been a consultant to the U.S. Centers for Disease Control and Prevention. I still am regarding potential terrorist agents that might be used in a chemical terrorist attack in the United States. I have secret security clearance to work on that and then on and off various other agencies.

Q And do you ever have occasion to deliver lectures to professional groups or toxicology organizations?

A Yes. I end up doing that quite a bit.

Q And could you just describe a couple of lectures and topics that you've done?

A Sure. I'll give you the two most contemporary examples, kind of the sense of what my life is like often. I came to these hearings virtually directly from Seville, Spain, where I was teaching part of an occupational and environmental toxicology course.

Immediately after leaving here, I go to Boston where I'm giving grand rounds at the University of Massachusetts Medical Center and then doing some teaching there, so it does not infrequently come up that I have to give lectures and teach in various professional settings.

Q And what professional organizations or honorary societies are you a member of?

A There's a bunch of them. They're pretty much the standard organizations in medicine and particularly in medical toxicology. I'm a member of the American Medical Association, for example, a member of the American Academy of Clinical Toxicology. That's the largest organization in the world devoted to clinical toxicology. I am a former president of that organization.

I'm a member of the American College of Medical Toxicology, which is the physician's only group for medical toxicologists and professional society physicians that specialize in medical toxicology. I actually serve on their board of directors. I'm a member of the American College of Occupational and Environmental Medicine. There's probably one or two others.

Q And do you currently serve as a peer

reviewer for any medical journals?

A I do.

Q Could you name a few?

A Sure. I end up doing a lot of peer reviewing, and I certainly reviewed quite a number of medical toxicology journals like *Clinical Toxicology*. I review routinely. I've got a review right now for *Journal of the American Medical Association*. I'm listed as a frequent reviewer for the *New England Journal of Medicine* and just a whole host of other journals, *Journal of Emergency Medicine*.

Q What do you do as a peer reviewer?

A Well, the peer review process is an extremely interesting, not quite perfect process but is probably the best we've come up with so far, and it works something like this: If an article is submitted for publication to a journal, it goes to the editor.

If it is a peer-reviewed publication, not all publications are peer-reviewed, and certainly all good publications are peer-reviewed, but if it is a peer-reviewed publication, what the editor then does is send the article out to experts in the field and say would you please look at this article, give us some feedback. Do you think it's worth publishing? Does the article have any problems?

Should it be revised, or is it really not a valid article, methodology, technique, the conclusion is wrong. Should this paper be rejected? Then you write up all that information in the form of a little report and send it in to the editor. The editor ultimately makes the decision about what to do with the article once they get input from usually two or three peer reviewers.

Q And you've published over 200 peer-reviewed articles on toxicology, is that correct?

A I wouldn't say all 200 are peer reviewed. If you look at my total number of publications, peer-reviewed articles, abstracts, book chapters and so on, yes, it's over 200.

Q Have you ever received money from a pharmaceutical company for a speaking engagement?

A You know, I have very early on when I graduated from my medical toxicology fellowship. My fellowship was from 1987 to 1989 and probably maybe in the year or two after that I did, and I don't think I have in the last 15 or so years, probably more.

Q And have you ever received money from a pharmaceutical company for research?

A I have received some money from pharmaceutical companies to do some research, yes.

Q Could you describe that?

A A number of years ago we did a study on when the newer class of antidepressants, the so-called SSRIs, Selective Serotonin Reuptake Inhibitors, came on the market, they replaced an older class of antidepressants, which were called the tricyclic antidepressants, and the first one on the market of this new class was Prozac, fluoxetine.

One of the problems with antidepressants, particularly from a toxicologist's point of view is that depressed people take them, and depressed people are prone to try to kill themselves, so one of the big issues was that the tricyclics, which a lot of depressed were taking are extremely, extremely lethal drugs if you overdose on them.

One of the advantages that we saw of the new selective serotonin reuptake inhibitors, Prozac, fluoxetine, Zoloft and so on, was that they seem to be much better tolerated in overdose. It was much harder to kill yourself on them, so we did actually a comparative study and demonstrated that in fact the selective serotonin reuptake inhibitors are much less dangerous in overdose.

That conclusion is now very widely accepted in the general medical community, and that's why

really people have shifted over to them. They don't work really I don't think any better than the old tricyclics, but they are much safer drugs to take, that kind of thing. I guess I should give you a more complete answer.

More recently, we did a series of clinical trials on a new antidote. The money didn't actually come from the pharmaceutical company, but it was from a FDA grant that we got in conjunction with a pharmaceutical company, and I was the principal investigator of those trials, and they were clinical trials that resulted in this new antidote being introduced into clinical practice, and it's widely used right now. I published both of those clinical trials in the *New England Journal*.

Q And have you ever testified before as an expert witness in a legal case?

A I have.

Q How many times?

A I suppose the first time I did it was sometime a year or two after I graduated from my medical toxicology fellowship, which was I said 1989, so probably over about a 17- or 18-year period several dozen times.

Q And have you served as an expert witness in

a legal proceeding on behalf of a pharmaceutical company?

A Yes.

Q And could you describe a couple of those?

A There have been a couple of different issues that I have. In fact, I gave testimony, I gave a deposition about four years ago, for example, in one case that involved allegations of vaccine-induced autism.

Q And is that the Easter case you were referring to?

A That's correct. That's the Easter case.

Q And who were you an expert for in that case?

A I believe I was actually for the defendants on the case. I believe that was GlaxoSmithKline if I recall correctly.

Q And did you give a deposition in that case?

A I did give a deposition in the Easter case, yes.

Q Did you testify at a trial in that case?

A Actually, there was no trial in the Easter case.

Q Do you know the outcome of that case?

A Yes. What happened was after a series of depositions were taken, the Judge dismissed the case

on a -- I think you call it a Daubert, if I'm using the term correctly, on a Daubert ruling. I read his ruling. Basically, he said he did not find that it was adequate scientific basis to continue on.

Q And you also testified as an expert witness in the Cedillo case before this Court, correct?

A That's correct.

Q Could you please describe your position as a Clinical Professor at University of Colorado?

A Sure. I have a number of duties. Clinically, they involve acting as an attending physician on our clinical pharmacology and toxicology consultation service at the university, which we see patients where there is any concern about adverse effects from any drugs or chemicals. In that context, In my role as the attending physician, what I primarily do is supervise the care. A lot of the primary hospital work is done by the residents and fellows on the service.

My role is to serve as the teaching attending to go over their care, to review their care and go over the issues with them. I also have other teaching responsibilities. I give a couple of lectures a month in various training programs, and then of course I'm expected to maintain a degree of

academic productivity in terms of publications and research and professional standing.

Q And you also have a private practice then?

A I do have a private practice.

Q What's the name of your practice?

A It's called Toxicology Associates. It's a single specialty group practice that is devoted purely to medical toxicology. We have three major aims at Toxicology Associates. The first and most important one is patient care. The second is research, and the third is teaching.

Q So you examine and treat patients with heavy metal toxicity?

A We do.

Q And have you ever treated a patient with mercury toxicity?

A I have.

Q Could you describe that?

A Well, I've actually treated quite a number of patients with mercury toxicity. I'll give you an example of some of the extremes, from one end to the other. One of the things that is sort of common up in the hills of Colorado, which still has some hints of being the wild west, is there are gold prospectors up in the hills, and there's some gold that you can pan

for. The problem is it's not pure gold.

So what you do if you have an ore and you want to get the gold out of it, you have to extract the gold from it, and you can take advantage of the fact that if you mix it with liquid mercury, quicksilver, that will extract the gold. The problem when you do that is then you have this liquid mercury and gold, and you need to get rid of the liquid mercury, and the way many people do it is they heat it. That will certainly volatilize the liquid mercury into the air.

The problem with doing that is that you generate extremely high mercury levels in the air and people routinely make themselves mercury toxic in doing so. They can be very, very, very sick. They can die from that degree of mercury exposure. I've had an opportunity to take care of numerous individuals, including families who I had to take care of an intensive care unit for a period of time because they were so sick from their mercury toxicity.

Another extreme is that sometimes you see people with fairly low-level exposures relative to these people that end up in the intensive care unit. For example, I recall one patient who was a dentist who bought a dental practice, and apparently the

person she bought the dental practice from was rather sloppy from his use of mercury amalgam and actually there was contamination of some of the rugs at the practice with mercury.

The dentist who bought the practice who was my patient used to vacuum the rugs in her practice. When you vacuum rugs that have mercury in them, you volatilize the mercury, and she actually developed a neurological syndrome and had fairly high mercury levels, but she wasn't nearly as sick of course. It's the people that we had treated in the ICUs. We treated her as an outpatient.

Ultimately, it turned out that her primary neurological syndrome wasn't really very much related to the mercury. I think she had MS. But at the time, we wanted to take the mercury component out of the picture so we had a more specific workup of whatever else was going on with her neurologically. So we've seen that.

I'd say these days for reasons that we'll talk about in a little while, I don't want to spend a lot of time on it now because it's a little bit off the point, but these days because of issues related to the internet and some of the labs that are out there I probably get a referral for a patient with concerns

for mercury toxicity once a week in my practice.

Q And have you ever examined or treated a child with autism?

A Yes.

Q Under what circumstances?

A Well, under a number of circumstances. I have treated them unrelated to their autism because they have a tendency to have pica, and I remember one case who was a significantly older autistic who overdosed in a suicide attempt. I treated several for lead toxicity related to the pica, and one thing that seems to be happening now in my practice related to a lot of the information out on the internet is that a lot of parents are very concerned about their children with autism and are concerned about the mercury issue.

I tend to see them on a one out of two circumstances. Often they'll go to their primary care pediatrician and ask them a bunch of questions. Is mercury an issue? Should my kid get chelated and so on, and the pediatrician will often say I don't know too much about this stuff. Let me send you to a toxicologist who might be better to answer your question.

I get a fair number of patients these days coming in that way, and the other side of that is we

also see patients who have gone to these sort of alternative medicine practitioners and are having their children chelated, and they're having all these different treatments, and at some point they may question or want to get a second opinion about whether this is actually the right thing to do.

And so, they'll go back often to their primary care pediatrician, and then their primary care pediatrician once again frequently says well, let me send you to a toxicologist who may be better informed with regard to this issue. I have a family in my practice right now that I'll be seeing as soon as I get back. I saw them just before I left, and I'll be seeing them in followup as soon as I get back related to this very issue.

Q And, Doctor, we'll move on. What is medical toxicology? I know you explained your education and background, but could you describe medical toxicology and we're going start the presentation with Slide 2.

A Sure.

SPECIAL MASTER VOWELL: Slide 2?

THE WITNESS: Yes. As you can see on this slide, toxicology in general is just simply the science and the adverse affects of chemical substances on living systems, so really anybody who studies any

effects of chemicals on living systems is basically doing toxicological studies. If they want, they can call themselves a toxicologist.

In contrast, when you see the term medical toxicology, that has a very distinct connotation because medical toxicology is a subspecialty recognized in medicine by the American Board of Medical Specialties like gastroenterology, cardiology and so on. It is a specific designation for a specific subspecialty in medicine. To be a medical toxicologist, you have to be a physician. You have to be licensed.

You have to have completed a primary residency and gotten board certified, and you have to have completed a two-year post-residency fellowship in an accredited fellowship program, after which you have to pass the certifying examination and then periodically recertify.

BY MS. RENZI:

Q And you're one of 350 physicians in the U.S. who are medical toxicologists, is that correct?

A Yes. We're an amazingly small group, a growing group, which is good because we are all way, way, way too busy.

Q Now, Doctor, how do you know if a chemical

is capable of causing a certain effect?

A It's important to realize that this is a fundamental question that comes up in medical toxicology all the time. You have a chemical exposure. Can this cause this effect, and in order to do that --

SPECIAL MASTER VOWELL: We've shifted to Slide 3 now.

THE WITNESS: Yes. In order to do that, it is important to not lose sight of the fact that there is a very fundamental methodology, scientific methodology, which has to be applied, and what I have done here on Slide 3 is to distill this scientific methodology down into its three major components. The first thing you want to know is what chemical was the person exposed to and at what dose.

Once you know that, then you can ask the question now that I know the chemical I'm dealing with, can that chemical cause the particular condition that the person has? I believe the legal concept here is called general causation, and if that chemical is not known to be capable of causing that person's condition, then we say it probably didn't cause his condition.

On the other hand, if the chemical is known

to be capable of causing that condition, then we go to the next question did in this particular individual that chemical exposure actually cause that condition. In other words, was it a dose, was the circumstances of exposure similar to those which are known from scientific studies to cause that condition, and if I'm correct the legal concept here is specific causation. If I can just add, it's a three-step process, and in my teaching I often use this kind of slide.

It's very easy to remember. We call it the what, can, did process.

Q Now, if a chemical is known to cause a certain effect, is everyone going to respond exactly the same way to the same dose?

A No. if we know a chemical exposure has occurred, then we want to know these two big questions: 1) is the chemical capable of causing the particular effect we're looking at, and if we know that, then we also want to know was the dose sufficient to cause that to occur, and the reason we look at dose is because almost all processes in medicine or in toxicology are dose related, that at very small doses almost nothing can be harmful.

At very large doses almost everything can be harmful, so you just have to look at each individual

substance, and where they fit on that so-called dosed-response curve. Here I've given --

SPECIAL MASTER VOWELL: We're on Slide 4 now. What we're going to be doing, Dr. Brent, is going back and listening to your testimony and reviewing the slides, and we want to marry that up with our notes.

THE WITNESS: I appreciate that, and I had a made a mental note to myself to do that, and I appreciate that reminder, and I will do my best to do so. As you can see here on the bottom of Slide 4, I give three examples of dose response curves. These are all of dose response curves, the so-called simple non-threshold curves. In other words, as soon as go up from zero, you get a little bit of a response, but different substances can have different shapes of the dose response curve.

Many substances, in fact most substances have what we call threshold dose response curves. In other words, it stays flat until you reach a certain dose, and then it begins to go up. On Slide 5, what I have done is I have generated what is supposed to approximate, which will give me some artistic license, a bell-shaped curve, and what that curve would represent, for example, the number of people in the

population that will respond to in some way to a chemical at a particular dose.

As you can see, it's a range of values that the most typical person will be near the middle of the curve, but as the curve drops off on either side, you will find some people on both sides. Some people respond at lower doses. Some people respond at higher doses, but generally speaking what we do see is this sort of bell-shaped curve.

Almost everybody fits into a statistical concept called two standard deviations around the average, around the highest values, and that's quite characteristic in the general population.

BY MS. RENZI:

Q And are there individuals that would be at the lower end of that bell-shaped curve?

A There are.

Q Are they a hypersusceptible population?

A No, no, not at all. This curve represents simply a range of values, some somewhat lower, some somewhat greater, but as I said tending to be clustered within about two standard deviations of the mean, and it just indicates some degree of individual variability. Now, a susceptible population is something very different. If you look on Slide 6, you

can see what the toxicologic definition of a susceptible population is.

A susceptible population is a population where that bell-shaped curve for that group of people is shifted. It has shifted way down to lower doses. Now, there are a number of specific instances in medicine where we know there are susceptible populations, and we see this phenomenon. When those susceptible populations exist, in general medical science is pretty good at identifying them, finding them and characterizing them.

Q And is there a known susceptible population for mercury?

A If you're talking about neurotoxic effects of mercury, I think it's fair to say that there has never been an identified susceptible subpopulation to neurotoxic effects of mercury in any form. There is no well accepted or generally accepted hypersusceptible population to mercury neuro toxicity.

SPECIAL MASTER VOWELL: And that was Slide 7.

THE WITNESS: That was Slide 7. Thank you.

BY MS. RENZI:

Q And aren't we all routinely exposed to mercury in different forms?

A Every single one of us every single day of our lives is exposed to mercury in various forms.

Q And do these various forms of mercury exposure result in mercury being deposited into our brains?

A Absolutely. If you look at every animal on the Earth, they have mercury deposit in the brain. If you look at every human being with our normal daily exposures that we all go through, we all certainly have some small burden of mercury in our brain, absolutely.

Q And this is Slide 8. Could you just talk about the different forms of mercury that we're exposed to on a daily basis?

A Sure. Sure, I'd be glad to. As you can see here on Slide 8, we get exposed to mercury from different sources. Our largest exposures are to organic mercuries, mercurials such as methyl mercury or ethyl mercury is from methyl mercury, and it is from dietary sources, so for all of us, if we look, for example, at some of our brain stores of mercury, the largest amount there comes from the diet.

We also get exposure as you know from vaccines, from thimerosal, which becomes ethyl mercury and causes some mercury deposition, and then there are

other various sources, mercury vapor, which can emanate from a dental amalgams, in airborne sources of mercury. What's important to remember however is if we look at all the mercury in our brains from all of these sources, which ends up ultimately getting deposited as this mercuric or mercury plus two ion that there's been testimony about.

You'll find that there is some deposited in the brain. It tends to be extremely small amounts. It's in what we call part per billion range, so it's a very small amount, and when a mercury ion is deposited in the brain from any of these sources, the brain has no way of distinguishing the source that it came from. It could be from methyl mercury. It could be from a vaccine. It could be from some other source. It is simply a mercury ion, and all mercury ions are exactly identical.

Q And how much mercury do we typically get from these exposures? We'll move Slide 8.

A Yes. If you look here on Slide 9, what I have done is I have listed our various sources of mercury exposure, and just to provide a perspective to get a sense of where the mercury that we are exposed to comes from, the average American diet is about 22 kilograms of fish a year, and some fish contain very

high levels of mercury, but it a conservative estimate for most fish is about half a microgram of mercury per gram of fish.

If you do a little bit of mathematics, you find out you can take 22 kilograms of fish a year, and in that fish there is 0.5 micrograms for every gram, 0.5 micrograms of methyl mercury for every gram of mercury, you come up with the fact that the average American consumer ingests about 11,000 micrograms of mercury from fish annually.

Now, if we look at infants, infants get most of their methyl mercury exposure through breastfeeding, and the average exposure of an infant to mercury from breastfeeding in the first six months of life is about 280 micrograms. Now, it's also important to note that there are other populations on the Earth, and this is for the American population, there are other populations on the Earth, which is a very well study where they eat much, much more seafood.

For example, in the Seychelles Islands where there has been a very long and ongoing study of the effects of mercury exposure due to diet, the average person eats about 62 kilograms of fish per year, maybe 3 times the amount of the United States, and

correspondingly their blood levels of mercury are about five to 10 times higher than what we see here in the United States.

Q Now I'd like to show you a slide from Dr. Aposhian's testimony, and it was Dr. Aposhian's Slide 54 from Petitioners' Trial Exhibit 2. I believe this Slide was taken from the Harry study, and I'd like to discuss that with you. The Harry study was done with mice, is that correct?

A Yes, it was done with mice.

Q And what does this study tell us about mercury deposition in the brain?

A This study injected mercury into mice and looked 24 hours later at the deposition of mercury in the brain, and as you can see it looked at it in terms of the percent of the dose that was administered to the mouse that remains as mercury in the brain, and they looked at it from methyl mercury. They looked at it following thimerosal administration, and they looked at it following ethyl mercury, and as you can see for each one of those there was some small percentage of mercury deposited in the brain.

In fact, if you look at the percentages, you get the greatest percentage retention in the brain from methyl mercury than from either thimerosal or

ethyl mercury, but you will get some deposition from all three of these sources.

Q And has there been a study with monkeys that looked at the same question?

A Absolutely. Probably a more relevant study would be done on primates. It's the study done by Dr. Burbacher, which was published in 2005.

Q And the Burbacher paper is Petitioners' Master List 26, and I'd like to turn now and have you look at page 1016, Table 1 of the Burbacher paper.

A Great. This table, Table 1 from the paper, as you can see is a description of what they actually did in the study, and the purpose of this study was to do a pharmacokinetic analysis of what happens to mercury when it's administered either as methyl mercury or as thimerosal to infant monkeys. They immunized infant monkeys with vaccines to which they added thimerosal, and they tried to sort of replicate what happens in a human.

Now, the immunization schedule there-you see, was on birth and then on day seven, 14 and 21, so at one week increments in a total of four doses. Now, obviously that's a much more compressed schedule than you would get in a human. The reason they did that is because the monkey's brain develops a little faster,

and they wanted to get various points of neurodevelopment during the time of the immunization.

They gave a dose of 20 micrograms of mercury per kilogram either as methyl mercury orally or as thimerosal in an intramuscular vaccine, and they gave that dose four times at birth, seven days, 14 days and 21 days.

Q And does the dose of 20 micrograms per kilogram for each vaccination, does that mimic childhood vaccination schedules?

A No, no. It's a substantially higher dose than you would get in a childhood vaccination. It's about three or three and a half times higher than a child gets in their first four vaccinations, zero, two-month, four-month, six-month vaccinations.

Q And why did they choose that particular dose, then?

A The reason they used the higher dose was because of concern for the fact that if they had used actual amount that was in the vaccine, there would be so little mercury that it would be below the limits of detection. They wouldn't be able to do their study.

Q And what is the basis for your conclusion about --

A Well, the Burbacher data was presented to

the institute of Medicine in 2004. Which was published before in 2004. The published version of the paper didn't come out until 2005, so Polly Sager from the NIH actually presented the Burbacher data to the IOM, and here you see the explanation. If I could just read this short little excerpt?

It says, "The dose that was chosen was not chosen because of any particular level. It was simply that they wanted to ensure that there was enough mercury that they would be able to measure it. You don't do a study like this and find out that the levels are below the levels of detection, so the animals were given 20 micrograms of mercury per kilogram either in the form of thimerosal or in the form of methyl mercury."

MS. RENZI: Special Masters, we filed actually the audio from the IOM. It was RML436, and this is just a text from that audio that's in front of you.

SPECIAL MASTER HASTINGS: All right.

BY MS. RENZI:

Q Did the Burbacher paper look at ethyl mercury deposition in the brain?

A It did.

Q And what did they find?

A Well, if we turn to Figure 7 of the Burbacher paper, you can see their measurement of mercury levels in the brain after these four injections of 20 micrograms per kilogram, and what they did is they gave all four injections, and then after the fourth injection they started to sacrifice the monkeys over a period of about 30 days and look at what happened to brain mercury.

They speciated the mercury such that they looked at both the inorganic mercury, in other words, the mercuric ions, and the organic mercury, the pure ethyl mercury, and you can see there are two major I think take home messages from this data. This shows that if you immunize monkeys at 20 micrograms per kilogram four times that the deposition of mercury in the brain gets to the point of about, as you see in the dashed line on Figure 7 of about just a smidgen over 10 nanograms per gram or parts per billion.

That is a sense of about the level of brain mercury that they got as a result of this immunization schedule. Now, since the immunization schedule used over three times as much mercury as a child would actually get in a vaccine, you would expect therefore that the amount of mercury in the brain that would be deposited from a vaccine wouldn't be upwards about 11

or 12 or 13 here, but would be about a third of this. It would be down around maybe two to three parts per billion in the brain.

If you look at the solid line, that shows the organic mercury, the ethyl mercury. As you can see, that level drops very quickly out of the brain. Some of it simply leaves the brain. Some proportion of it obviously become inorganic mercury, but the end result is as you can see that the inorganic mercury levels in the brain following vaccination using their relatively higher dose protocol is a little over 10 parts per billion, which would translate for vaccine to maybe two to three parts per billion in the brain.

That is the expected brain burden that based on the Burbacher study from a vaccine.

SPECIAL MASTER VOWELL: Doctor, can I interrupt because I'm not sure I caught everything you were saying there?

THE WITNESS: Please.

SPECIAL MASTER VOWELL: What does the dashed line represent versus the solid line?

THE WITNESS: Right.

SPECIAL MASTER VOWELL: I want to make sure I understand this while you're here.

THE WITNESS: I appreciate your asking

because it's an extremely important question. The dashed line is an inorganic mercury, the Mercury 2 ion that is in the brain.

SPECIAL MASTER VOWELL: Okay.

THE WITNESS: And that's the part that does not come out and that stays there.

SPECIAL MASTER VOWELL: The mercuric mercury?

THE WITNESS: Yes, the mercuric mercury, and that in their experiments is a little over 10. Probably it would be closer to two or three parts per billion following the vaccine. Then the solid line is the ethyl mercury.

SPECIAL MASTER VOWELL: The ethyl mercury that gets into the brain and does not convert to mercuric mercury?

THE WITNESS: Well, what the solid line shows is that the ethyl mercury itself drops down over time and one out of two things could be happening to cause it to drop down. Some of it obviously leaves the brain. Some of it may become mercuric mercury. what's interesting to note however is as that line drops, we don't see the mercuric mercury line going up quite a bit, so that's suggests that a good deal of it is leaving the brain and not being converted to

mercuric mercury. Did that answer your question?

SPECIAL MASTER VOWELL: It did. Thank you.

BY MS. RENZI:

Q The Burbacher study also looked at methyl mercury deposition in equal doses, is that correct?

A It did.

Q And what did they find of that?

A Well, if you look at the next figure, which will be Figure 4 of the Burbacher study, this shows what they found when they looked at mercury concentrations in the brain on the exact same protocol 20 micrograms per kilogram, but this time methyl mercury orally, and what you see there is once again the dashed lines is the mercuric ion, the inorganic mercury, and the solid lines is the organic, the methyl mercury.

The amount of inorganic mercury in the brain is the same general ballpark, actually a drop lower, than what they found for when they gave thimerosal, which may be eight or seven parts per billion, and the amount however of the organic mercury, the methyl mercury in the brain is about 10 times higher, and so the total mercury burden there is about 100 parts per billion.

If you look at what happens over time, if

you look at the inorganic mercury, it stays pretty much the same just like after thimerosal. The dashed line there they drew, that looks like it has a little bit of a downslope, but there's no statistically significant drop over time. If you look at the methyl mercury itself, that level does not change either over time unlike the ethyl mercury, the level quickly dropped.

The methyl mercury stays quite constant at about 100 parts per billion over time, and an in fact in his statistical analysis, if you compare the points on the methyl mercury or the solid line, the left point when they first started looking and the points all the way over on the right 30 days later or 28 days later when they terminated their experiment, these two points are not statistically significantly different from each other.

In other words, they were not able to demonstrate that there was any reduction in the methyl mercury level over time following methyl mercury injestion, so this shows that methyl mercury and ethyl mercury have rather different pharmacokinetics in the brain such that with equivalent doses you get about the same amount of inorganic mercury, but you get probably 10 times as much organic mercury with methyl

mercury.

Now, we don't know the ultimate fate of that methyl mercury. Some of it will probably be demethylated to inorganic mercury. Some of it may flux out of the brain. Some of it may just stay there as methyl mercury.

Q Let's take a look at the methyl mercury and ethyl mercury graphs side by side.

A Right. So this shows the actual comparison side by side with the thimerosal, Figure 7 on the right, and the methyl mercury on the left. Notice that the Y axis because there's so much more methyl mercury than there was from the ethyl mercury. The Y axis are a different. For methyl mercury it goes up to 1,000. For ethyl mercury, it goes up to 100, and as you can see the amount of inorganic mercury is roughly comparable. Thethyl mercury, however, it drops quite rapidly. The methyl mercury in contrast stays quite constant.

SPECIAL MASTER VOWELL: Dr. Brent, a question for you.

THE WITNESS: Please.

SPECIAL MASTER VOWELL: Does the mode of administration have any impact? I notice from these slides that it was oral methyl mercury and

intramuscular injection of thimerosal. Are we comparing apples and oranges, or are they both going to be apples?

THE WITNESS: No. I think again that is a very good question, and I think the answer to that in science, you only know what you study, so this tells us that for equivalent doses, oral methyl mercury, as you would take in in food, gives much higher brain levels than intramuscular thimerosal.

SPECIAL MASTER VOWELL: So we're mimicking the way people get it rather than trying to compare --

THE WITNESS: That's exactly right. That's exactly right. We don't know if the result would be the same if the thimerosal was given orally or if the methyl mercury is given intramuscular.

SPECIAL MASTER VOWELL: I'm sorry to interrupt, but I have to ask the questions before I lose my train of thought.

THE WITNESS: Please do.

BY MS. RENZI:

Q And didn't they also look at blood levels for ethyl mercury in the Burbacher study?

A Yes, they did.

Q And I'll refer to Figure 5 on that paper.

A Yes. There's a point I'd like to make about

this. As we saw in the prior slides, for equivalent doses, you get significantly higher mercury in the brain from methyl mercury, but there is another factor as well, which is that because they gave their injections a week apart, there was not an opportunity for the thimerosal from the prior injection to clear from the blood before they gave the next injection unlike what happens in humans.

If you inject two months later, there's no more ethyl mercury in the blood. It's gone, but here since they gave them at weekly intervals, there was a progressive accumulation effect, so you see with each progressive injection here in Figure 5 of the Burbacher paper that the peak mercury goes up and up and up, so there was accumulation kinetics, which is not what you would see with a human, so that actually further inflated the brain mercury that they saw in the thimerosal group than you would see in a human.

So I think putting all that together it's quite safe to say that probably based on the Burbacher data that you would predict that brain mercury level related to the immunization schedule, two, four and six months for a slowly immunized child would probably give in the range of maybe two parts per billion in the brain of mercuric mercury.

Q And we see the mercury deposition in the brains of animals. How much do we typically find in human brains?

A Well, it's been studied, and I think I have that on the next slide.

Q And this is Respondent's Master List 294, Figure 9.

A Here you see a study of brain mercury levels, and on the bottom three entries are simply autopsy data from various populations, the general population of Germany, the general population of Sweden, and in human neonates who died in Rochester, New York, and if you look at these three numbers, that gives you a sense of what normal brain mercury levels are.

As you can see, normal brain mercury levels are probably something in the range depending upon what population you look at, maybe 15, just sort of in the middle of that, or maybe anyplace from two to maybe 30 parts per billion. That is what you would typically expect in the human brain as a background level of mercury.

Q And how would a vaccine affect, a thimerosal vaccine affect, these numbers?

A Well, we talked about the fact that if you

look and say the first six months of thimerosal related vaccine from the Burbacher data, you would expect that there would be an additional increment of maybe two parts per billion of mercury to that, maybe three.

Q And where would brain levels from let's say the Seychelles Islands be on this graph?

A Right. If you remember when we were talking about how much mercury people are exposed to, that one of the populations that has been studied quite a bit because of their very large amounts of mercury ingested in the Seychelles Islands where their fish consumption is about three times the United States. Their blood mercury levels run five to 10 times what we see here in the United States, and so their brain mercury concentrations have been studied as well.

As you would expect, it's significantly higher than we get here in the United States, and as you see in this figure, their mercury levels look like -- it's a little hard to tell the exact number. It may be 200. Yes, maybe 150, 200 parts per billion in the Seychelles Islands as their normal levels, and this value represents what is referred to in toxicology as you can see there on the charts the no observed effect level.

We have a concept in toxicology, and that is, what dose of a substance can you give, what's the highest dose of a substance you can give without observing any adverse effect, and we call that the no observed effect level. As you can see there from this analysis, that the highest level of mercury in the brain that has been studied in which there is no observable effect is in the Seychelles, and it's probably in the range of 150 and 200 parts per billion mercury in the brain.

We don't know how high you have to get above that before you start getting effects. As you can see on this diagram it shows that there is some subtle effects that are found at maybe 1,100 parts per billion in the brain in animal models.

Q And do you know if there's a greater rate of autism in the Seychelles given the relatively high amount of mercury in the brain?

A Yes. I do know the answer to that. To my knowledge, there's no publication on that, but I read Dr. Clarkson's report that was filed with this Court where he addressed that very issue. Dr. Clarkson has been the principal investigator in this study of the Seychelles, and here as you can see from his report he states, and I don't want to read the whole thing.

"In some 30 years of detailed pediatric and neuropsychological tests on large cohorts of infants with continuously elevated mercury blood levels," meaning in the Seychelles, "I have found no evidence of an increased prevalence of autism. Admittedly, we did not specifically look for autistic children, but the many neurocognitive tests we carried out, none of which uncovered neurological deficits would surely have detected such cases."

Q And that's Respondent's Exhibit K at pages 5 and 6. Doctor, what about the Faroe Islands? How did the mercury intake compare with the Faroe Islands to the Seychelles?

A Well, the population on the Faroe Islands is similar to the Seychelles Islands. It's another heavily fish-eating population there, they're out in the north Atlantic, and although their pattern of fish eating is slightly different from the Seychelles, they too are very heavy fish eaters just like the Seychelles' population. Their blood levels run considerably in excess to what we see in the United States or close to what we see in the Seychelles, so they get fairly similar mercury exposure in the Faroe Islands as well.

Q And do you know whether there's an increased

rate of autism in the Faroe Islands?

A Yes. That actually has been formally studied in the Faroe Islands, and here you see the paper that studied it. It's the publication by Ellifsen, which is, looks like RML 138, and they showed as you can see there that of children aged --

SPECIAL MASTER VOWELL: I think that may be RML 130.

MS. RENZI: 130.

THE WITNESS: I'm sorry. I'm sorry. Of the children aged eight through 17 years, which is the population they looked at, 0.56 percent had childhood autism, Asperger syndrome or atypical autism. The male/female ratio is just under six to one. The prevalence of autism in the Faroe Islands was very similar to that reported in western countries.

Therefore, if we look at these populations that have much, much, much more inorganic mercury deposited in their brain, there were hundred well over parts per billion deposited in the brain compared to what we see here in the United States. There is no increase in autism. There's 0.56 percent. It's about 1 in 200 cases. Actually, slightly less than our current rate here.

BY MS. RENZI:

Q Is there any evidence that autistics have more mercury in their brains than nonautistics?

A No. There has never been a study that suggested that autistics had more mercury in their brain than nonautistics. Therefore, I think it's fair to say that any reasonable conclusion based on the existing scientific data tells us that a couple of parts per billion of mercury in the brain that we receive through thimerosal-containing vaccines cannot possibly be a significant contributor to brain mercury concentration.

Overwhelmingly much more comes from other sources such as methyl mercury, and it's all --

SPECIAL MASTER VOWELL: That was Slide 10 and Slide 11 we've moved to now.

THE WITNESS: Yes, and on Slide 11 I have articulated that. There's no possible way that a very small amount a mercuric ion or inorganic mercury from thimerosal containing vaccine can exacerbate cause or contribute to the effect of the much greater amount of the mercuric ion in the brain from nonvaccine-related sources.

BY MS. RENZI:

Q Doctor, I'd like to move on now. During this trail, we've heard a lot about various studies

that were in vitro studies. Could you please explain what an in vitro study is?

A Yes. On Slide 12, I have put down some information about what an in vitro study is. Now, we generally talk about two different types of studies in the biological sciences. We talk about in vivo studies and in vitro studies. An in vivo study is a study done in an intact organism. It could be an animal. It could be a human.

The in vitro studies on the other hand are studies that tend to be done outside of the actual organisms, done in the laboratory maybe with cells and culture, for example, in a petri dish. They're studies that are done in the laboratory environment, and it's important to remember that the laboratory environment is a highly artificial environment, and the circumstances in the laboratory environment are dramatically different than the circumstances in the body, in vivo.

If we're looking at a neuron or any other particular type of cell in the laboratory, that cell is existing in an environment, which is radically different from the environment that they are in the body, and that has dramatic ramifications for the way you interpret these studies and the vulnerability of

cells in vitro.

Q So, Doctor, then can you use in vitro studies to extrapolate how a chemical will react in a human?

A No. You can use in vitro studies to generate hypothesis about effects a chemical might cause in humans, but because the environments are so radically different, you cannot reach conclusions. For example, if I take some cells and just simply incubate them with water in the laboratory, I'll kill those cells. Now, one just certainly cannot conclude that water is lethal to neurons in humans, and this is shown on Slide 13.

SPECIAL MASTER VOWELL: Thank you.

THE WITNESS: This difference between the laboratory and the whole body environment is such that the cells in the laboratory become much, much much more vulnerable. I'll give you an example. Here we're talking about mercury and mercurial compounds like thimerosal or ethyl mercury.

In the body, we have a cell in the brain whether it's a neuron or an astrocyte or any cell in the brain is in an environment where there are a large number of protective molecules, glutathione, thiols of all different kinds, metallothionein, which I know

there's been testimony about, a number of other proteins that bind and therefore inactivate the mercury molecules, those are not present in in vitro studies.

In vitro studies is just a cell and the free mercury, so the cells are exposed to a much higher concentration of free mercury than they would ever be exposed to in the brain because in the brain it is all tied up. The molecules in the brain bind these exogenous substances, and by doing so prevent them from interacting with cells, and so there's very little free mercury or free whatever compounds they're studying that can actually interact with cells, and that's the problem with in vitro experiments.

If we go to the next slide, we see therefore that as a result of that while in the brain almost all the mercury is bound and inactivated, and there's very little free mercury, it's only the very small fraction that's free that can interact with cells. In in vitro systems, all the mercury that was there is free and can interact with cells.

That's why as Dr. Deth pointed out in his study that there was this sort of artificial in his presentation to this Court that there was this sort of artificial environment and in reality you would

typically expect the concentration of mercury in free form that is able to interact with cells in his words to be vanishingly small. Therefore, you can never assume that effects you see in vitro occur in vivo.

BY MS. RENZI:

Q Now, you mentioned Dr. Deth's study, and he did an in vitro study with Dr. Waly in 2004, and that's Petitioners' Master List 257. Could you please tell us about that study?

A Sure. This study is a classic example of the problem with in vitro studies. What the Waly and Deth study was was a study where they took some cells in culture, in a petri dish, in the lab, and it was a neuroblastoma which is from a tumor line of cells, and they put thimerosal in with these cells, and they found that it inhibited this enzyme, which we heard quite a bit about last week, called methionine synthase.

But that's just thimerosal interacting directly with the cells. Dr. Deth himself pointed out that's not what would happen in vivo. In vivo what thimerosal was there or ethyl mercury was there, the level would be vanishingly small that would be free to interact with the cells. The other thing, which is another example of the kind of artifact you can get in

the in vitro environment, the test tube environment, is that his data only occurred when there was no copper present in the medium, in a copper-free medium.

If he added a small amount of copper to his medium, that activity all came back, so it's a function of insufficient copper in the medium. Now, the reason that's a limitation is because in the body we have very significant amounts of copper. We would never be in a copper-free environment.

Q And this is Slide 16 that we're on now.

A So he created a system that could never occur in the body, and in fact we made it a little bit more like what we see in the body by adding back some copper. Then it essentially vanished. Those are some examples of how the artificiality of an in vitro experiment, in this case Dr. Waly and Dr. Deth's experiments, impact the results. The other thing I should point out is that remember he was studying the enzyme methionine synthase.

Methionine synthase in that particular cell line that they used is a defective methionine synthase, so it's not typical of the methionine synthase you would expect to see in neurons, so even if it applies, we wouldn't know if it had anything at all to do with neuron data. As of now, there is no

peer-reviewed published evidence that autistics in any way have a defective methionine synthase.

Q And didn't the 2004 IOM specifically look at the Waly/Deth study?

A They did. That study was presented, and they specifically looked at it.

Q And what did they conclude?

A Well, so here they're talking about the methionine synthase experiments of Waly in 2004, which is the one publication they have on this, and they say, "The authors hypothesize that disruption of this pathway, i.e., the methionine synthase pathway, by thimerosal leads to autism, ADD and other neurodevelopmental disorders. However, the committee is aware of no evidence that autism is caused by alterations in this biochemical pathway."

In addition, the evidence that several important toxicants disrupts this pathway and that is involved in many physiological effects weakens the argument that thimerosal might cause autism through this mechanism.

Q And that's Respondent's Master List 255 at page 136 and 137.

A And I might just point their reference here to the fact that many important toxicants affect this

pathway is that the Deth experiment didn't only look at thimerosal. They showed a whole bunch of things inhibit that enzyme.

Q Now, you've also heard at this trial about the 2005 in vitro study of Dr. Jill James, and that's Petitioners' Master List 007. Can you please tell us about that study?

A Sure. There's a slide on it, Slide No. 17, and as you recall, there's been some testimony here that this study stands to support the proposition that thimerosal administration lowers glutathione levels. Actually, this was an in vitro study using some tumor cells, and what was important about the tumor cells that were used in the James' study is that normally this cell line has about one thousandth the amount of glutathione than normal cells have.

That cell line is highly deficient in glutathione to begin with. Then what was done is thimerosal was added in vitro to culture these tumor cells in micromolar amounts. Now, you would never get a brain cell exposed to micromolar amounts of mercury through ethyl mercury. The amount of mercury in the brain, which we talked about it parts per billion translates to nanomolars, about 1,000 times less.

If you look, that's what I just pointed out,

so there's very high amounts of mercury in cultured cells that have very low levels of glutathione to begin with, and the allegation was that amount of mercury then injured the cells and reduced their glutathione levels. Remember, you'd never see first of all cells in the brain that would have such low levels of glutathiones. Cells just don't have those low levels of glutathione. Cells may have 1,000 times more glutathione typically.

In vivo, instead of micromolar amounts of mercury, which they use in the experiment, the cells would actually be exposed to very vanishingly small amounts, nanomolar amounts of mercury. The other thing about that experiment is they actually didn't even show that there was a statistical difference mostly because they didn't do a statistical analysis to that point.

Q And did the authors of the James' study intend to mimic what happens in vivo following receipt of a thimerosal-containing vaccine?

A No. They made it clear that they weren't even trying to do that.

Q And I'll refer to page 3 of that study.

A Yes, and this is directly out of that study where they say, "Acute high dose exposures to the

thimerosal micromoles per liter", which is micromolar, far in excess of anything you'd ever see in the brain, "and cultured cells were used to study mechanistic aspects of thimerosal toxicity and not intended to mimic exposure of developing brain cells in vivo to thimerosal in vaccines," which would typically be nanomoles per liter.

Q Dr. Brent, are your opinions about in vitro studies well-accepted in the greater general medical community?

A I think they generally are, absolutely.

Q Did the IOM comment on the validity of in vitro studies?

A They did.

Q And I'm referring to Respondent's Master List 255 at page 140. What did they say?

A Quoting the IOM, they said, " The hypotheses reviewed by the committee were that vaccine-induced autism represents the end result of a combination of susceptibilities, possibly genetic, to immune dysfunction or to abnormal mercury metabolism." They then go on to point out, "Demonstrating an adverse effect of mercury in vitro does not readily translate into a physiological argument."

Q Thank you.

A Science would be much easier to do if we could do all our experiments in test tubes, in the culture.

Q Now, you've read Dr. Aposhian's report in this case, is that correct?

A I have.

Q And on what did he base his hypothesis that thimerosal-containing vaccines cause autism?

A Well, if you remember Dr. Aposhian's report, he based his hypotheses on six pillars that he said supported his position, and these are listed here on Slide 19. They were the Adams tooth study, the hair studies by Dr. Holmes, and they also made reference to the poster by Hu, the Bradstreet/Geier chelation study, the fact that as he put is to quote him, "the most beneficial treatment for autism is chelation," the Hornig study and a study by Courchesne dealing with post-natal loss of brain cells in autism.

Q And have you assessed these pillars on which Dr. Aposhian's hypothesis is based?

A Yes. If you'll notice, the first five of these pillars deal with toxicologic questions. The sixth doesn't, so I looked at the first five.

Q And I'd like to go through then those first five, and the first one was the Adams study?

A That's right. Dr. Aposhian's first pillar was the study by Adams on tooth mercury.

Q And we're on Slide 20. Could you describe that study?

A Well, that study actually follows on the heals of other data related to tooth mercury. For example, if you go to Slide 21, you can see that tooth mercury has not been uniquely studied by Adams. There was a big study by Tvinnereim, which is RML 488 and described here on Slide 21, and this was a study that looked at primary teeth. The Adams study as we'll see in a moment looked at primary teeth, and they looked at over 1,200, almost 1,300 primary teeth, and they studied the mercury concentration in those teeth.

The mean concentration of mercury in primary teeth they demonstrated is about 0.27 micrograms of mercury per gram of tooth, and they found that there were various factors that affected the amount of mercury in a tooth: 1) whether there were carries present in the tooth or not, not talking about obviously mercury-containing amalgam, but just carries in general; 2) the type of tooth.

For example, there was a higher concentration of mercury in molars than there were in other teeth, and also that there was a coassociation

between the lead in a tooth and the mercury in a tooth. This study was done, and then came the Adams study, which you see I believe in Slide 22, and the Adams study looked at primary teeth from 16 children with various autism spectrum disorders, not necessarily regressive disease and 11 controls.

As you can see, 81 percent of the cases of autism was male. Only 45 percent in the controls were. We'll come back to that point in a second. If you look at the tooth mercury concentration, Adams points out here that they found higher tooth mercury concentrations in the autistic group than in the control group.

Now, I'll call your attention to the fact that if you remember the Tvinnereim study that the primary teeth, which was a much larger study and a much better sample, the amount of mercury you typically expect in primary teeth is about 0.27 micrograms per gram, so even the autistics were lower here than the baseline in the bigger study.

The other thing is if you look at the tooth mercury levels, excuse me, the tooth lead levels, you can see that there is an increased amount of lead in the autistic teeth compared to the controls, although it's not a statistically significant result. I think

the group was much too small to be able to demonstrate statistically significant results related to that point.

Q And what other problems did you find in your review of the Adams study?

A The Adams study has a number of problems, which I have listed here on Slide 23. First of all, it's a small and nonreplicated study. It's not really a criticism so much as to say you can't take too much away from it, but there are some bigger issues with it. One thing is as you saw the ratio of males to females is very different in the autistic group, in the control group, and they did not control for that. As I recall, even Dr. Aposhian gave testimony here that that might influence tooth mercury concentration.

The other thing is what do you make of this? Tooth mercury has never been shown by anybody to reflect body burden of mercury, so nobody really knows what to make of this. Also, if you'll recall from the Tvinnereim study, it's very important to control for the type of tooth because different teeth have different concentrations of mercury. They did not do that in the Adams study. There are statistical tests by the way. It was an invalid statistical test, so I'm not sure you can draw any statistical results from

it.

The other thing to remember is that pica is common in autistic children and that they did not really control for that. As we saw, there was numerically a higher level of lead in the autistic children's teeth. If you remember from the Tvinnereim study, there's more lead, there's more mercury in the teeth, so they needed to control for that.

More concerning was that we know from the big study that tooth mercury levels are supposed to be approximately 0.27 micrograms per gram typically in the general population of primary teeth, and all the numbers here were much lower. The autistics were lower, and the controls were lower than the numbers we would expect.

Q I'd like to turn now to Dr. Aposhian's second pillar, and what was that pillar?

A Dr. Aposhian's second pillar dealt with the hair study.

Q And that's Slide 24, and what studies did he rely upon?

A Well, he relied primarily on the study of Holmes. Although, he did make reference to a poster by Hu. Slide 25 describes the Holmes study. What the Holmes study did is it measured first baby hair

mercury in autistics, and what it showed or what it reported was that there was a statistically significant difference, that asterisk that I have on the slide next to autistics means statistically significantly different, amount of mercury in the autistic hair than in the control hair.

Now, once again the Holmes study was not just regressive autism. It was the whole spectrum, and if you look, the autistics had about 0.47 parts per million of mercury in the hair. The controls were about 3.6, much, much higher. The Holmes study therefore concluded that hair excretion patterns among autistic infants were significantly reduced relative to control, and this was cited as support by Dr. Aposhian for his so-called efflux theory or poor excreter theory.

Now, there's a couple of things to note about the Holmes study. If you look at what would be expected hair levels of U.S. children in the United States. It's typically based on the large NHANES study, which was a very large study that represented samples of populations. You expect it to be about 0.22 parts per million. Now, if you look at the Holmes study, the controls, the normals was 15 times greater. It was 3.6.

There is no reasonable explanation for how that can possibly be, and if that's the autistic, we're much, much closer to the normal than the normals were, so that raises a bit of concern about the Holmes study.

Q Now, Dr. Aposhian testified that the Holmes study was confirmed by the Hu study, which he referred to as the MIT study, and that's Petitioners' Master List 16. Could you please briefly describe the Hu study?

A Yes, sure. On the next slide, which is Slide No. 26, it talks about this abstract that was published by Hu, et.al., that was cited as the study supporting the Holmes study, and what they did is they looked at hair mercury concentrations in three individuals that had autism. If you look actually at the study, here is what they say.

"The ASD hair samples were taken from three individuals affected by ASD, two of whom are under treatment for heavy metal detoxification. The treatment protocol requires complete exclusion of seafood from these individual's diets. The third ASD individual consumed seafood at least once per week and a regular diet," so they looked at three individuals, two of whom were on a seafood-free diet, and lo and

behold what did they find?

If we go to the next slide, which is No. 27, we see that two of the three individuals who were on the low seafood diet, they had low hair mercury levels. No big surprise. The one single AUTISTIC individual who was on a normal diet had a hair mercury concentration of .4 parts per million. It's almost exactly what you'd expect from the general population.

Q Have there been other hair studies that have attempted to replicate the Holmes study?

A Yes, there have been five. These are five subsequent studies that have been published that have attempted to replicate the Holmes data, and not a single one of them could replicate that data.

Q And Dr. Aposhian's third pillar was a chelation study?

A Yes.

Q That was a Bradstreet/Geier study. Could you please describe that study?

A Right. I would be glad to. On Slide 30, you see a description of that study. This was a study published in the *Journal of American Physicians and Surgeons*. The *Journal of American Physicians and Surgeons* I should point out is almost the only journal I've ever encountered in my scientific career that is

not listed in the National Library of Medicine. In that study, they gave a mercury chelator succimer, which is DMSA for three days, and they measured urine mercury level, and they looked at two populations.

As you can see in this little table on Slide 30, they looked at a population that had diagnosis of autism or PDD on one hand, 55 individuals, and then they looked at eight so-called control individuals. However, the control individuals were individuals who were brought to his practice because the family had concerns about mercury toxicity in those individuals.

As you can see, the urine mercury was about 6.4 in the autism population and was about one microgram per gram of creatinine in the control population from which they concluded that the autistics have a body burden of mercury which can be mobilized by giving a chelator to cause enhanced excretion.

Q And what were the problems you found in your review of the Bradstreet/Geier study?

A There are a lot of problems with the Bradstreet/Geier study, and here you see some of them on Slide 31. Remember that the controls who excreted less mercury were individuals who were brought to the practice because of concern about mercury toxicity.

It's likely they were probably on a low seafood diet, and there was no control for diet in that study.

Also, by the way because I looked at the statistics, and I saw as we'll see in a minute the huge ranges of values, and I found it hard to believe it was truly a statistically significant result, and I tried to reproduce it every way I could, and I could not following their methodology show that their results were statistically significant. The other thing is there was no assessment of compliance.

These people were thought to be taking the chelator over a short period of time. There was no assessment of whether they really did or not. If you look at the paper, and you look at the range of values, they're huge, and they're overlapping.

Here you see Table 1 of the Bradstreet/Geier study, and if you look at mean mercury concentrations in the cases and the controls, they vary from zero to almost 59 micrograms per gram, and in the cases in the controls from zero to six, so how there can be such a difference I have no idea. That's such a wide range, but you certainly can't reach any conclusions from that kind of study. Now, if we go to the next slide --

SPECIAL MASTER VOWELL: Which is 32.

THE WITNESS: Which is No. 32, and you look at the urine excretion in the cases, those patients who had autism or ASD had urine levels that are fairly typical of what you might expect for anybody given a chelator whether they were autistic or not. The problem is you really can't interpret it because this was an experimental study on chelation, and experimental chelation studies always require that you do a nonchelated urine to see what effect the chelator has.

You do a nonchelated urine, then you give the chelator, and then you do a chelator urine to see what the difference is. They did not do that. Further, on Slide 33, in the Bradstreet study, they didn't exclude patients who had prior chelation, so that may have influenced the result, and it's also important to know that DMSA mobilizes mercury that is stored in the kidney.

Almost all the mercury that is excreted found in the urine following a DMSA challenge comes from mercury that's stored in the kidneys, so all this tells us is about mercury in the kidneys. It doesn't really say anything about body burden, so you really can reach too many conclusions based on this kind of study. As I mentioned, it's published in a non-

National Library of Medicine recognized journal.

Actually, the editor of the journal at the time was from SafeMinds, and most importantly that there was a better study published in a more legitimate scientific journal that attempted to replicate these results, and that study showed no significant difference in mercury excretion between autistics and controls.

BY MS. RENZI:

Q And what was that study?

A That was a study by Dr. Soden.

Q And that's Slide 34?

A That study is described on Slide 34 where they administered DMSA to children with autism and to normally developing children and in fact were not able to verify the Bradstreet/Geier results. If you look at that study, you see their conclusion, which is, "In the absence of a proven novel load of heavy metal toxicity, the proportion of autistic participants in this study whose DMSA-provoked excretion result demonstrate an excess chelatable body burden of arsenic, cadmium, lead or mercury is zero."

Q And we'll move on then to Dr. Aposhian's next pillar, his fourth pillar that he relied on for his hypothesis.

A Yes. Slide 36 shows Dr. Aposhian's fourth pillar where he says that the most beneficial treatment for autism is chelation therapy, and I did assess that.

Q And what did you determine?

A Well, you can sum it up very quickly on Slide 36. I couldn't find a single study in the peer-reviewed medical literature or scientific literature that demonstrates that chelation therapy is beneficial in autism. No such peer-reviewed published study exists.

Q And Dr. Aposhian's fifth pillar of his hypothesis, what was that?

A Dr. Aposhian's fifth pillar was the Hornig mouse study, which I believe there's been some testimony about already.

Q And what is your assessment of the status of the Hornig study?

A I have summed that up very succinctly on Slide 38. The Hornig study could not be replicated. Berman tried to replicate that study and could not replicate it. Dr. Aposhian agrees the study could not be replicated. Dr. Mumper agreed the study could not be replicated. I certainly believe the study could not be replicated, so I don't think there's anything

more we really need to say about the Hornig study.

Q And based on what we've just talked about, in summary, what conclusions have you reached about Dr. Aposhian's six pillars that he says taken together support his hypothesis?

A Well, here we have the six pillars. As I said, I'm only going to discuss the first five of them, so as you can see, the Adams tooth study is not really supportable. The hair studies do not support any difference in hair levels between autistics and controls. The Bradstreet/Geier chelation study was a highly defective study, which a better study could not replicate.

There is no support for the statement that in terms of a published study in the scientific literature shows that the most beneficial treatment for autism is chelation, and the Hornig study could not be replicated, so at least out of the five pillars that I've looked at that constitute the basis for Dr. Aposhian's theory or his hypothesis, those five pillars cannot be supported.

Q I'd like to just change gears for a minute and turn your attention to a different topic. You've heard testimony throughout this trial about thimerosal-containing vaccines causing oxidated

stress, which leads to autism, is that correct?

A I have. I have.

Q And we'll look at Slide 40.

A Yes. The mercury from thimerosal-containing vaccines induce the oxidative stress hypothesis.

Q Is there any support for this hypothesis?

A Absolutely not. I can sum it up on Slide 41, and I'll tell you there has never been a study showing that the amount of mercury in a thimerosal containing vaccine whether individually or collectively can cause, can exacerbate or can contribute to oxidative stress or oxidative damage. In fact, such an assertion is impossible because if you'll remember we get much more inorganic mercury load from diet, from methyl mercury.

There's only a very small amount that comes from the vaccine, so were this assertion true, then breastfeeding, eating some chicken, eating some fish would cause much more oxidative damage than you would get from a thimerosal-containing vaccine, and clearly the simple act of breastfeeding or eating chicken or fish does not induce significant oxidative damage.

Q Doctor, you've also hear allegations about ethyl mercury from thimerosal-containing vaccines inducing neuroinflammation. In your expert opinion,

is there any support for that hypothesis?

A Well, I have never seen a study showing that the amount of mercury in a thimerosal-containing vaccine whether we're talking about individually or collectively can modulate the immune system in any way, and it's the same thing. Were this true, then we would have the same situation. We'd get neuroinflammation or a modulated immune system from breastfeeding, from eating chicken, from eating fish whether you get much more of a load of the mercury and the inorganic mercury.

This is an extremely confusing question for me because if you'll recall, Ms. Renzi, I was questioned quite a bit on cross-examination in Cedillo about the allegation that the mercury from thimerosal-containing vaccines act as an immunosuppressant, and now I'm hearing testimony that the allegation is that mercury from thimerosal-containing vaccines is an immune stimulator, is proinflammatory. And it's neither.

Q And there's also been some testimony about mercury porphyrins. Can you tell us a little bit about mercury and its relationship to porphyrins?

A Yes. If you go to Slide 43, this sums up the porphyrin data. There have been two studies,

which I know have been referred to in these proceedings, and that is the studies of Woods and the studies of Nataf, and these studies assess porphyrin profiles. Now, porphyrins are part of a biochemical pathway that all of our cells do. Many of the important molecules that are used in our cells are derived from porphyrins, and so our cells make porphyrins.

The studies of Woods and Nataf look at the porphyrin profiles in terms of what porphyrins are excreted in the urine. That reflects renal porphyrin synthesis, so what they're studying is actually porphyrin synthesis in the kidney. There is no evidence whatsoever that renal porphyrin profiles reflect mercury neurotoxicity, and in fact renal porphyrin profiles are not an accepted or validated test for mercury toxicity.

The only people I know that do them are alternative medicine practitioners, DAN doctors, people of that ilk.

Q Petitioners in this case have had urine mercury determinations done, and there's been testimony from Dr. Mumper about what they show. Can you tell us as a medical toxicologist how to properly interpret mercury urine concentrations?

A Absolutely. On Slide 44, I have a little primer here on how to appropriately assess urine mercury concentration. The only accepted, the only validated test for assessing mercury exposure except for the immediate short period of time after the exposure when you might look at blood levels is a urine mercury, and the only accepted type of urine mercury type, the only type that's been validated, the only type that's interpretable is a non-chelated specimen.

There are plenty of reference ranges for what is normal in the population for a nonchelated urinary mercury excretion level. There are on the other hand no validated reference ranges for chelated mercury levels, so they are essentially uninterpretable. We know that since we all have mercury burdens in our body if any of us would have taken mercury chelator our mercury urinary excretion would go up.

That's an absolutely expected resulted, a well-documented result, but it's very variable from person to person, so there are no accepted reference ranges. It's an uninterpretable result.

Q And what are some of the studies that demonstrate the chelators will increase urinary

mercury excretion in normal people?

A Yes. This has been demonstrated over and over again. I must admit that I didn't even think that this would even be an issue in these proceedings, so I had to hastily sort of put together this slide, Slide No. 45, but this is an example of studies that I happened to think of that show that if you take nonmercury poison, nonautistic individuals, you will enhance mercury excretion.

I think there might be one typo on this slide, and I'm sorry. I just realized it this morning. It's the Grandjean study. I think it might be 1997. I apologize for that. That's the fifth bullet on Slide 45.

Q And I'd like to put up some of the lab results from William Mead in this case. Specifically, it's Petitioners' Exhibit 15 at page 118, and without going into the specifics of this lab result, could you please just read what the bottom of this lab report says and tell us the significance of that?

A Right. This is a lab result from Doctor's Data, Incorporated where they reported urine metal levels, and as you can see in bold on the bottom it makes this very point. It says, "Reference ranges are representative of a healthy population under

nonchallenge or nonprovoked conditions, so that's the reference range, and so when you are assessing a urine mercury level, as they point out here, you look at it under nonprovoked conditions.

Q And what pattern of urinary mercury excretion do you typically expect to find in normal individuals?

A If you go to the next slide, Ms. Renzi, and this is Slide No. 46 I believe and just look at the top, you can see that what would normally be expected is that if you're an older person, and you don't have an excess mercury burden, and we assess your urine mercury excretion, it's going to be in the normal range.

However, if we have given you a chelating agent, obviously it's going to increase, and so normally you would expect that if you provoke urine excretion with a chelator, you will find excretion above the reference range, which is for nonprovoked urine.

Q And you've also looked at the urine mercury test for Petitioners Jordan Kind and William Mead, and what did they show?

A Well, they showed pretty much exactly what you'd expect for the normal population, that their

unprovoked specimens are normal. Yet, when they give chelators, most of them are increased. Now, this is of great concern to me because as I look through the medical records, and I hear Dr. Mumper's testimony it's data like this that has been used as an excuse to subject these children to chelation therapy where in fact the data supports that their urine mercury status is totally normal.

Q We also heard Dr. Mumper refer to red blood cell element testing in support of her causal hypothesis, and I want to show you William Mead's test, and that's Mead Exhibit 5 at page 5, which is a red blood cell element lab report from Doctor's Data. Is this report an accepted and appropriate test in determining toxicity?

A No. Red cell metal levels are kind of lab results you can get from Doctor's Data. It is not a type of lab that we would routinely use in medicine to make these determinations. There's no validation of how to interpret the results.

Q And then I'd like to turn your attention to King Exhibit 1 at page 36, and this is another Doctor's Data lab test specifically of fecal metals test, and I'll ask you the same question. Is this an appropriate measure for determining toxicity?

A No. It's the same thing. This is not a test you would do in routine medical practice. It is once again the type of test you can go to Doctor's Data on the internet and get, but it is not one that has any validated results that one can really use in a meaningful fashion.

Q And also Dr. Mumper testified that hair tests in older children were not indicative of mercury toxicity, I believe that you did state that babies' first haircut tests were useful measurements in determining mercury excretion. I'd like to now take a look at some of the hair tests performed on William Mead and Jordan King, and the first one we'll look at is William Mead, Exhibit 5, page 44. What does that lab test show you?

A Well, this is a hair level test from Doctor's Data. I will tell you that I probably get two patients a month referred to me by their primary care physicians because the person went and got a hair test to Doctor's Data. They almost always come back with very high levels of all kinds of things on it, and nobody ever knows how to interpret it, and I interpret it.

I end up having to see these patients and am ultimately able to demonstrate that none of this has

any validity when we do the appropriate testing, but this is an example. Here you see this test of William Mead. If you take this test at face value, what does it tell us? It tells us that William Mead has elevated levels of aluminum, antimony, arsenic, bismuth, titanium and molybdenum in his hair.

There is no reasonable reason why anybody would have these kinds of hair levels, these kinds of elevated hair levels. If you look at the next lab result --

Q And that's from King Exhibit 1, page 46. Can you describe this test, please?

A Yes. This is Jordan King's hair testing result from Doctor's Data when he was two years old showing elevated levels of antimony, arsenic, bismuth, cadmium, lead, mercury, silver, tin, titanium, chromium. molybdenum, boron, lithium and rubidium.

Q And finally, I'd like to take a look at the hair test from Jordan King Exhibit 7, page 36. Could you explain those lab results?

A Same profile. Here you see his hair test shows he's above the reference range for aluminum, antimony, arsenic, bismuth, cadmium, mercury, silver, tin, uranium, molybdenum and boron.

Q Dr. Mumper also testified that the low

bicarbonate levels in Jordan King's test results showed metabolic acidosis and oxidative stress, and one example she referred to is the King Exhibit 1 at page 58, and we'll pull that up.

A Yes. She testified about several of these lab results of the Petitioners.

Q Could you just comment on the appropriate interpretation of this test?

A Yes. I would have to say that as I listened to that testimony I was very concerned when I heard that testimony. This test that you see here highlighted is a test for serum bicarbonate, also sometimes referred to as serum CO_2, carbon dioxide, and as you can see, when this blood was drawn the carbon dioxide or the bicarbonate level was slightly low, which Dr. Mumper did testify was indicative of acidosis and metabolic stress.

Now, one way that you can drop the carbon dioxide levels in your blood very, very quickly is you just breath a little faster. The more you breath the faster you breath you breath off carbon dioxide. One hundred percent of the time, if not 100 percent, 99 percent of the time when you draw blood on a child, they start breathing fast as any parent knows, and sometimes much faster if they're crying, and so CO_2

levels always drop.

It is an anomaly to do a blood test on a child who is awake when you draw the blood and actually find a normal CO_2 or bicarbonate. Interpreting this 100 percent normal and expected results as a metabolic acidosis indicative of oxidative stress is something that is a misinterpretation that no reasonable pediatrician or physician would ever make.

Q Now, Dr. Brent, the opinions that you've expressed in your testimony today are they widely accepted in the medical community and by well-respected agencies?

A I believe they are, yes. Here you have on Slide 47 a list that I've put together of governmental and well-regarded nongovernmental agencies that have looked at this issue and have concluded that there is no demonstrable relationship between ASD and thimerosal administration.

It includes the National Academy of Sciences, Institute of Medicine, American College of Medical Toxicology, American Academy of Pediatrics, World Health Organizations, U.S. Centers for Disease Control and Prevention, European Medicines Agency, which essentially functions as the FDA for the EU and

the American Academy of Family Practice.

Q Doctor, has any governmental agency or well-regarded nongovernmental agency ever taken a position to the contrary?

A None.

MS. RENZI: Thank you. I have no further questions.

SPECIAL MASTER VOWELL: We've been at it for about two hours now. Would you like to take our mid-morning break before you begin your cross-examination?

MR. WILLIAMS: Yes, please.

SPECIAL MASTER VOWELL: All right, Mr. Williams. We'll reconvene then at 11:35. I'm sorry. You're right. Thank you. I'm not adding well today. 11:20. Would that work for you? I just started to ask if the 35 was going to confuse you, and it obviously will. 11:20?

MR. WILLIAMS: Sure.

SPECIAL MASTER VOWELL: Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER VOWELL: All right. We're back on the record. Dr. Brent is back on the witness chair, and I remind you that you're still under oath, Dr. Brent. Mr. Williams?

THE WITNESS: Thank you, Special Master

Vowell.

MR. WILLIAMS: Thank you, Special Master.

CROSS-EXAMINATION

BY MR. WILLIAMS:

Q Good day, Dr. Brent.

A Good day, Mr. Williams.

Q I would like to start by just going straight into that infant monkey study by Dr. Burbacher and Dr. Clarkson that you talked about on direct in which you talked about in your report. Let me just put it up on the screen and go through it here. First, you do agree that Dr. Clarkson was one of the investigators and co-authors of this paper, right?

A Yes.

Q And this was a study that was funded by NIH, right?

A Correct.

Q Are you aware of any other primate experiment that has tried to look at the effect of thimerosal-containing vaccines on the brain other than this one?

A There might have been. This actually didn't look at effects on the brain. It looked at kinetics and the deposition of mercury in the brain.

Q Well, the study had looked at effects on the

brain, they just haven't published those results yet, right?

A I don't know what they haven't published.

Q You haven't talked to Dr. Clarkson about it?

A No.

Q Okay. You are aware that this study only looked at half of each infant monkey's brain and that the other half was reserved for pathological analysis to see whether there was immune activation?

A I have no idea what further analysis they have done. I've not seen anything on it. There is nothing published. I only know what they published.

Q So are you aware of any better study, any other study we have of an experimental nature that looked at the pharmacokinetics of thimerosal-containing vaccines in the brain?

A A better study? No.

Q Doesn't the vaccine manufacturers around the world, they use the same special of monkey for preclinical trials of vaccines, don't they?

A They may.

Q You don't know?

A I haven't compared the species.

Q Well, they use the same genus, is that right?

A Well, they use primates. They use monkeys.

Q Okay. They use the Macaca genus of monkeys, don't they? There are several species of those monkeys.

A That's correct.

Q Okay. So it's widely accepted that this species of monkey is a good model for humans given that we can't do experiments on children themselves?

A I don't know if I would say that. I would say that it is the best model we have as far as we know.

Q Okay. Now I want to talk to you a little bit about the relevance of the FDA reference standard for methyl mercury as it applies to the thimerosal situation. This study discusses that. This paper this discusses it. If we could go to the lower left-hand column where is starts, "Recent reports have indicated...?"

SPECIAL MASTER VOWELL: The lower left-hand column of what page.

MR. WILLIAMS: Of the first page.

SPECIAL MASTER VOWELL: Okay.

BY MR. WILLIAMS:

Q Again, this is Petitioners' Master Reference Exhibit No. 26, and I'm on page 1, and you see where

it says, "Recent reports have indicated that some infants can receive ethyl mercury in the form of thimerosal at or above the US EPA guidelines for methyl mercury" depending on the size and so forth, and then the paper in the next column goes on to talk about the quantity of ethyl mercury that infants receive, if you could highlight to the top of the second column Scott.

Do you see where it says, "Other estimates have indicated that the schedule could provide repeated doses of ethyl mercury from approximately five to 20 micrograms per kilogram for the first six months of life?"

A Yes.

Q Now, you testified on direct that you thought 20 micrograms per kilogram was far above the possible human infant exposure. Are you disagreeing with Dr. Clarkson here?

A No. I think you're misinterpreting the statement, and I think it's fairly well accepted that a fully immunized infant is going to get 187.5 micrograms of mercury over about the first six months. You can divide that by say the typical body weight of a six-month old, which is about eight kilograms.

You will probably get about 24 micrograms

per kilogram of mercury, which is about a third of what was given in the Burbacher experiment as per the testimony, which you can see very clearly if you simply go back to Table 1 and add up the numbers. It's very clear that that's the case.

That was the testimony that was given as a matter of fact before the IOM that that indeed was the case because if they gave the amount of mercury that was actually in the vaccines, they ran the risk of having undetectable amounts.

Q You're talking about Polly Sager's statements at the IOM? I don't think she was testifying.

A Well, she presented the Burbacher data to the IOM.

Q Right. I'll get into that in a minute because I've got a copy of your slides, but for purposes of the general causation question here that the Special Masters have to consider putting aside the Mead and King cases, don't you agree that on the Grande bell-shaped curve of human infants you're going to have a lot of them that are small, some are pre-term, and they're going to get this much equivalent of ethyl mercury as the top level here in the monkeys?

A Eighty micrograms per kilogram over six

months?

Q Twenty micrograms per kilogram of each dose?

A Yes. Eighty micrograms per kilogram over six months. Eighty micrograms per kilogram over six months, no. I have not seen any data. It would have to be an extremely, extremely small infant, even at six months.

Q If you go to the very bottom of that column where it says Magos (2003), you'll see that the authors are reviewing what the sort of consensus was before this study was conducted where it said that Magos concluded that because ethyl mercury clears from the body faster than methyl mercury and that the brain to blood mercury concentration ratio established for methyl mercury will overestimate ethyl mercury in the brain after exposure to ethyl mercury, and also because ethyl mercury decomposes faster than methyl mercury, for all those reasons Magos had concluded that the FDA reference dose probably overestimated the risk of ethyl mercury, is that right?

A Correct.

Q And that's always been your position, right?

A Correct.

Q It was in your report?

A Correct.

Q I think it's very into your testimony the Cedillo when Special Master Vowell tried to pin you down on that point that whether you were saying that the reference dose for methyl mercury was an overestimate or an underestimate of the risk of ethyl, and you said it's definitely an overestimate, right?

A I don't recall that exchange, but I'll accept that it occurred.

Q Okay. So the initiated this study to assess whether an experiment which showed those things to be true in these primate infants?

A Well, I mean, I can't speak to what was in their mind when they decided to do this study. I can tell you what the study is, and the study is a pharmacokinetic analysis after administration of methyl mercury versus ethyl mercury.

Q And then in the right-hand column on page 1, where it says the dosages and schedule of administration of mercury, and we'll highlight that for a minute, the study says that the doses in the schedule of administration of mercury were chosen to be comparable with the current immunization schedule for human newborns. Are you saying that you disagree with the authors of this study that that's what they were trying to model?

A As I mentioned before, as you see there, if you continue that highlighting taking into consideration the faster growth of the Macaque infant, that's why they gave the immunizations at birth, seven, 14 and 21 days, at weekly intervals, as opposed to two-monthly intervals. That's what they took into consideration. Look, the immunization doses schedule for humans is well known. It's noncontrovertible, and it is not the same doses schedule that was used in this paper. That's the only point I was making.

Q Well, let's see if the authors agree with you about that point. Let's turn to page 2 in the first-hand column under the Materials and Methods section, and if you go down to the end of the second paragraph where it says the dose, this is Dr. Clarkson talking. He says, "The dose of 20 milligrams per kilogram was chosen based on the range of estimated doses received by human infants receiving vaccines during the first six months of life."

You just disagreed with the authors of this paper on that point I take it?

A All I can do is reiterate the points I've already made. The doses in infants in the first six months of life are well known, and they're well accepted. I don't think there's been any testimony

given that an infant in the first six months of life gets 80 micrograms per kilogram in a vaccine. This was chosen to mimic the immunization schedule of an infant in the sense that the doses were given at time intervals corresponding to a relatively quicker evolution of brain developmental stages.

It was given in vaccines to which they added thimerosal, but it was given with enhanced amounts of thimerosal so that they would actually have a detectable level of mercury in the brain.

Q You've been consulting with the manufacturers on this issue for how many years now?

A I have consulted with them in the past. I'm not really doing much active consulting with them now. I gave a deposition as I mentioned in 2004.

Q Have the manufacturers ever tried to mimic the vaccination schedule for thimerosal containing vaccines in a primate model to try to do a better job than these NIH-funded investigators did?

A Well, I don't think doing that experiment would be a better job. I think the premise of your question is actually incorrect. I mean, the numbers speak for themselves. The numbers speak for themselves, and we can bring them up and look at them again. Were they to give the amount that is in a

vaccine, they would run the risk...

A monkey experiment is a very expensive experiment to do, and you have to sacrifice monkeys, and they would run the risk of doing this whole experiment and then finding they couldn't detect the mercury in the brain from the amounts present in the vaccine. I'm not sure that would be a better experiment.

Q When Polly Sager made this statement, that was February of 2004, right?

A I don't remember the date.

Q Well, let's look quickly at her slide, which is Defense Reference Master List No. 436. You see the date down there in the bottom right-hand corner?

A Yes, I do. It looks like February 9, 2004.

Q Okay. And that's the same meeting that you were quoting from her testimony as you said, right?

A I believe so.

Q Okay. Now, Polly Sager, she's not an author on this paper, right?

A No.

Q And she's a strong advocate of the vaccination program around the world, isn't she?

A I have no idea.

Q Do you know whether she opposed the removal

of thimerosal from vaccines?

A I have no idea.

Q Do you know why she was presenting some of this data to the IOM committee instead of any of the authors of the study?

A She said the authors weren't there, and she was presenting the results on their behalf.

Q Now, when she presented her data in February of '04, the authors had not yet done the speciation studies, right?

A I don't know if they did or not.

Q Well, have you reviewed her slides to see if she presented the speciation data?

A I don't recall that she presented the speciation data. Whether they had done it by then and not passed it on to her or not, I have no idea.

Q And if the reason for choosing the 20 microgram per kilogram dose was as you say when the authors published this paper almost a year later, don't you think that they would have put that in the paper?

A They put the doses that they gave in the paper.

Q No the reason for the doses being a detection problem as opposed to an attempt to mimic

the program?

A Well, you can only put so much in a paper. You're limited in test size that a journal will let you publish. You can't put every single detail of your experiment. Whether that's an essential detail is something that needed to be put in is debatable. I don't think they ever were able to foresee somebody coming along and trying to make the allegation that somebody gets 80 micrograms per kilogram in the first six months of life from a vaccine.

Q So you don't believe that these authors, even though you think it's the most important point about the paper that they chose this dose for technical reasons, not to mimic the program, you don't think they would have put that in the paper?

A It's an important point in the paper in terms of this discourse that we are having regarding the testimony that came up here. Whether that is the most important point of the paper in the real world, in terms of the global issue of what the paper showed I think is debatable.

Q Now, let's go look at some of the measurement results. If we turn now to page 4 of the paper, in the middle column of that at the very bottom of the this part here that I'm showing. We'll

highlight that for a minute. Doesn't this show that the washout rate for methyl mercury in the infant monkeys was longer than the washout rate for the adult monkey study that this group had done previously?

A Is that the sentence that begins with "T1/2?"

Q Yes.

A "As long as in the previously reported $T_{½}$ of the brain..." That's what it says, yes.

Q And it's referring to the Vahter papers here. Those are the adult monkey studies that this group had done before, correct?

A That's correct.

Q So that the infant monkeys' brains took a longer time to get rid of the mercury than the adult monkey brains had done?

A Well, there's two potential interpretations of that. That is one. The other interpretation is that in the Vahter study the dosing schedule and the administration of methyl mercury was radically different than in this study, and that could have affected its kinetics as well because if you remember in the Vahter study, these animals were being dosed with very, very high doses of methyl mercury on a daily basis, so that is a very different scenario and

could create a very different kinetics in the brain.

Q Bolus doses are different than continuous doses?

A No, but the Burbacher study was a low-dose study given intermittently, and the Vahter study was a high-dose study given continuously.

Q Well, we'll get into the Vahter study in just a few minutes.

A Sure.

Q Let's look at the measurements of the inorganic mercury in the infant monkeys exposed to methyl mercury. This is in the third column of the same page at the end of that column. Blow that up Scott. We can blow that up. It says that the concentration of inorganic mercury, and we're talking here about Hg++, right?

A That's correct.

Q The concentration of the inorganic mercury in the brain samples was below the quantifiable limit of the assay, which was seven nanograms per milliliter. That's seven parts per billion, right?

A Yes.

Q In eight of the 17 methyl mercury-exposed monkeys, and the average concentration of inorganic mercury for those monkeys with values above the

detection limit, which was only 10 of the monkeys, did not change significantly over 28 days of washout. It was approximately seven to eight nanograms per milliliter, right?

A Correct.

Q But if you were trying to estimate what the average concentration was, wouldn't it be appropriate to consider those monkeys where there was a below the detection limit and assume that this average of seven to eight is actually probably lower than that?

A Well, yes. I mean, you could reach that conclusion. This is a perfect illustration of the fact that had they actually gone to lower concentrations of mercury in their administration and used, for example, what is used in the vaccine schedule, how you can so easily fall under the limit of detection, but yes, you can conclude that maybe it was five. Maybe it was four of inorganic mercury.

Q Right. Five or four. Then let's look at eh measurements of inorganic mercury in the brains of the infant monkeys who were exposed to thimerosal. That's on the next page, which is page 5 of this paper in the right-hand column. Now, it says that the inorganic form of mercury in these monkeys was readily measurable as opposed to the problem they had with

detecting it in some of the brains of the methyl mercury monkeys, correct?

A The inorganic mercury.

Q Right.

A You have to remember that the reason for that is that methyl much more slowly becomes demethylated to inorganic mercury, and so as we saw at the end of the experiment when there was this very high concentration of methyl mercury still left in the brain that indicated that there had not yet been complete transformation of methyl mercury to inorganic mercury unlike the situation with ethyl mercury where you get a relatively fast transformation, and that's what their figure shows.

Q Well, if we jump down to the figure that you showed, Figure 7 just below this, which is the graph of the rate of drop in the organic ethyl mercury, even if the last test day, which was I think 28 days after the last vaccination, so 49 days into the experiment there was still measurable amounts of ethyl mercury in the brains of these infant monkeys, too.

A Yes. Remember, as we look at Figure 7 of the Burbacher paper, they got their last immunization immediately before the first point on the right, and as you can see, those levels are dropping quite

radically or quite steadily I should say. There is still some left, but nothing at all comparable to what is left following methyl mercury that can still get deethylated or demethylated, which was the point I was trying to make.

Q Now, if we go to the next page, page 6 of this study, in the first full paragraph that starts "Although the initial distribution volume..." what they found was that the model for methyl mercury elimination didn't really fit the ethyl mercury elimination data, correct?

A Well, there you're referring to elimination from the blood, and yes, the model for methyl mercury, elimination from the blood, is different. It's a so-called one-compartment model where the elimination of ethyl mercury from the blood is a so-called two-compartment model.

Q If we highlight where it says the second slower phase of washout and highlight that down to the bottom of that paragraph, you see it says the second slower phase of washout could also represent the gradual biotransformation of ethyl mercury.

The presumed principal organic form of mercury after a thimerosal administration to mercury-containing metabolites that have a different tissue

distribution or are more slowly eliminated, so they were suggesting that one explanation of this bi-phasic result in ethyl mercury was because it was distributed into the tissues differently than methyl mercury and was being more slowly eliminated from those tissues.

A Remember, the point that I think we both just agreed on was that the elimination kinetics of methyl mercury are different from ethyl mercury, and ethyl mercury follows a two-compartment model, which means that essentially it's eliminated in two phases, and so you get two separate half lives, shorter half lives and a longer half life in the blood, a natural membrane, and so always when you do these kinds of pharmacokinetic analyses, you always try to assess the implications of your data, and so yes.

It shows a two-compartment model, and so it is reasonable to speculate that the ethyl mercury as it leaves the blood may be going to other tissues. Remember now we're talking about the blood and not the brain, and in fact we know from a lot of other data that ethyl mercury preferentially will accumulate in the kidneys compared to methyl mercury, so it's a perfectly reasonable statement.

Q And then the last statement here says, "Further investigations of the disposition fate of

thimerosal derived mercury should address these issues." Do you know whether the manufacturers have done any studies to further address these issues?

A I have no idea what the manufacturers have or have not done. I'm not sure what question they would be answering.

Q Do you know whether the government has funded any studies to do further investigations on the fate of ethyl mercury in infants?

A In the peripheral tissues? No. I know there's a great deal of data out there once again that ethyl mercury tends to concentrate in the kidneys, but beyond that, I'm not sure that is a question that is very high in anybody's mind.

Q Well, Dr. Clarkson and Dr. Burbacher thought it should be investigated when they published this paper, correct?

A They put that statement in there? I don't know.

Q You think they put it in there, and they didn't mean it?

A Maybe Dr. Burbacher was applying for a grant to do that? I have no idea why they wrote that.

Q Let's go to the second column and the last couple sentences of the first paragraph where it's

talking about the brain-to-blood partitioning. It explains first that mercury exposure between thimerosal and methyl mercury is largely driven by their differences in systemic disposition kinetics, the blood level. That was the point you were just making, right?

A The mercury exposure?

Q The tissue distribution depends on blood level, that's the peripheral distribution?

A Yes.

Q Yes, and then they go on to talk about the brain-to-blood partitioning, and they say that the average brain-to-blood partitioning ratio of total mercury in the thimerosal group was slightly higher than that in the methyl mercury group, 3.5 versus 2.5, right?

A Right.

Q And thus the brain-to-blood mercury concentration ratio established for methyl mercury will underestimate the amount of mercury in the brain after exposure to thimerosal, correct?

A That is correct. They're not interchangeable figures.

Q And therefore the FDA reference standards would lead to an underestimation of the risk of

neurotoxicity from ethyl mercury because of this difference of brain-to-blood ratio, wouldn't it?

A No, because, they were talking about... when they used this 3.5 figure, they were talking about one particular point in time. If we go back to the amount of mercury that remains in the brain following the administration of an equivalent dose of methyl mercury or thimerosal, and that's in those two figures you've showed, and I don't know if you want to bring them back up. We can look at them again.

Q I'll get to that in a minute.

A It clearly shows that there is much more after an equivalent dose methyl mercury in the brain than ethyl mercury.

Q The very next paragraph in this same column if we pull it up, it says, "The large differences in the blood mercury half life compared with the brain half life for the thimerosal-exposed monkeys indicates that blood mercury may not be a good indicator of the risk of adverse affects on the brain, particularly under conditions of rapidly changing blood levels such as those observed after vaccinations. That's the bolus dose effect, right? You're not getting a steady dose of thimerosal. You get a large bolus dose, and then you have these rapidly changing values.

A No, you don't get a large bolus dose. There is no way that you get a large bolus dose. You get an intermittent dose. You get an intermittent low dose. As I mentioned earlier, over the course of six months, just through breastfeeding a child gets about 250 micrograms of mercury through methyl mercury. They do periodically get some small increment of mercury from a vaccine, but it's certainly not a large bolus dose compared to the total amount that they're getting a baseline basis from just the breastfeeding alone.

Q The breastfeeding source of mercury, that's all methyl mercury, right?

A Absolutely.

Q Okay.

A Most of it.

Q Let's go on to the very next sentence here where it says, "The blood concentrations of the thimerosal exposed monkeys in the present study are within the range of those reported for human infants after vaccination," and they cite the Stajich study, which I think was the only one that was available at the time, so if this 20 microgram per kilogram dose was not mimicking as the author says it was the study, wouldn't you have expected to see the blood range out of the range of human infants?

Why would it be comparable if this is not a good model?

A You miss the point. They were looking at brain levels. If you remember the Harry slide, brain levels are way less than one percent of the total administered mercury, so yes, you might find it in the blood, but they were looking for, and an essential part of the Burbacher experiment was to assess brain kinetics, and no, they probably would not have seen it in the brain based on those blood levels.

Q No. I don't think you answered my questions. It says, "The blood concentrations of the thimerosal-exposed monkeys and the present study are within the range of those reported for human infants..." Isn't that evidence that this is a good model of what's happening in the human infants when they get the same blood kinetics as in the human infant study?

A Yes, they might have achieved with doses similar blood levels, but you wouldn't have detected them in the brain.

Q And then it goes right on to say, and we'll come on down so we can see the rest of the next couple of sentences here, "The data from the present study support the prediction that although accumulation of

mercury in the blood occurs over time with repeated vaccinations, accumulation of mercury in the brain of infants will occur.

"Thus, the conclusions regarding the safety of thimerosal drawn from blood mercury clearance data in human infants receiving vaccines may not be valid given the significantly slower half life of mercury in the brain as observed in these infant Macaques." Now isn't that evidence that the FDA reference standard was an underestimate of the neurotoxic risk of thimerosal compared to methyl mercury?

A No. There's no way that that could be the case because once again remember that for any equivalent dose, you get far greater deposition of mercury in the brain from methyl mercury than from ethyl mercury. You can't look at blood levels. You look at what's in the brain.

Q Sorry. I didn't mean to interrupt you.

A That's okay. You look at what's in the brain, and the brain data clearly shows that you get much more mercury in the brain from methyl mercury than from ethyl mercury, so you can't use the methyl mercury standard for ethyl mercury or thimerosal.

Q Let's be clear when we say mercury in the brain what we're talking about. You're talking now

total mercury in the brain.

A Absolutely.

Q And the concern here was inorganic mercury in the brain.

A Well, what happens to total mercury in the brain it becomes inorganic mercury.

Q And once it's inorganic mercury in the brain, it doesn't matter to the brain anymore whether it came from the methyl mercury or the ethyl mercury or you happen to eat some mercury chloride, you're still going to get some in your brain, right?

A Well, I'll agree with you it doesn't matter whether methyl mercury or ethyl mercury. Mercuric chloride doesn't get into the brain very well, so that's kind of a bad example, but I agree. The brain has no way of knowing if any given inorganic mercury atom comes from methyl mercury or ethyl mercury.

Q Okay. And then the very next paragraph starts, and we can highlight it, "There was a much higher proportion..." Yes, that's it. "There was a much higher proportion of inorganic mercury in than in the brains of methyl mercury monkeys. Seventy-one percent of the thimerosal mercury was inorganic, whereas only 10 percent of the methyl mercury was inorganic, correct?

A Right, and that's because although the inorganic levels are about the same, there was much, much less ethyl mercury and much more methyl mercury left behind, so yes, there was a smaller percentage of the methyl mercury because there was so much more in the brain as methyl mercury that was inorganic.

Q In fact, the conclusion of this paragraph says, "This suggests that the dealkylation of ethyl mercury is much more extensive than that of methyl mercury." You do agree with that though?

A It's faster.

Q Right. And then it says that previous reports have indicated that the dealkylation of mercury is a detoxification process that helps to protect the central nervous system, and they cite Dr. Magos' 2003 and '85 papers. Now, do you still believe that to be true, that is a detoxification?

A I believe there's data that the organic form of mercury can cause toxicity, and in fact in the organic form, methyl mercury caused more neurotoxicity than ethyl. That's in the Magos paper. On the other hand, there is also data, and you can see that in Vahter that inorganic mercury caused a similar toxicity, so I think both of these cause toxicity.

Q So you agree that Hg++ is neurotoxic in some

doses?

A Yes.

Q And it's neurotoxic in those adult monkey studies because it provokes neuroinflammation, correct?

A Well, we'll get into that in a minute. It's important to remember, and if you want to discuss the Magos study, we can go to that now. It's up to you. You're asking the questions, but again I should point out however that when we talk about neurotoxicity, we're talking about toxic manifestations, so inorganic mercury does certainly have the capability of being neurotoxic, but it requires a sufficient dose to be neurotoxic.

That was my point about saying you can have well over 100, 150, 200 parts per billion of mercury in the brain without having neurotoxicity. Now, if you would see some toxicity threshold, then yes, you will develop neurotoxicity, but you have to exceed the toxicity threshold.

Q So just to be clear, you argued about the doses necessary to provoke it. You do agree that inorganic mercury in the brain can provoke neuroinflammation, which can be toxic if it's bad enough?

A You know, in terms of neuroinflammation, I guess I would put it like this. If you look at the Vahter study, for example, and I think that's --

Q And we will.

A I think that's what you were referring to when you were talking about neuroinflammation.

Q We're going to go there in just a moment.

A Okay. If you look at the Vahter study, they detected some cellular effects. We can argue about whether they saw neuroinflammation or not. The other issue is the significance of those effects. You have to remember that the Vahter monkeys were behaviorally normal, and so the chemical effects that were observed at the Vahter study, the high doses, represented some process. Whether that was a harmful neuroinflammation or not I think is questionable, but I think the fundamental message there is that even at these very high doses in the Vahter study, the animals were completely normal as far as anybody can tell.

Q They were all mature adults?

A Yes.

Q They were not developing brains in infants?

A They didn't study developing brains in infants.

Q That's right. Don't you think that a

developing infant brain is likely to be more susceptible to neuroinflammation induced by inorganic mercury than the adult brain?

A I'm not exactly sure why would you say that.

Q I'm asking you. I'm not saying anything --

A I don't know any data that allows me to reach that conclusion.

Q So you think that based on what you know that the amount of inorganic mercury in a developing brain is validly assessed by what happens in an adult brain?

A No.

Q No?

A What I'm saying is that I don't know of any data that anybody could reasonably rely on to say that an infant brain is going to be more vulnerable to neuroinflammation than an adult brain.

Q Okay. Fair enough.

A It might be. I just don't know of any data that supports that. Although I will point out I'm not a neuroinflammation specialist. I can only talk about mercury, and certainly I know no data in the mercury literature that supports that.

Q But on your what, can, did analysis that you had on your slide, if the what is inorganic mercury in

the brain, we got that here, right?

A That's correct.

Q That's here. And if the disease at stake or the adverse effect at stake is microglial activation and astrocyte death, we have evidence from the adult monkey studies that inorganic mercury causes that too, right?

A Well, the adult studies show microglial activation and astrocyte death, yes. To what degree that represents neuroinflammation, you might want to ask a neuroinflammation specialist.

Q Okay. Well, at least you are conceding here I believe that inorganic mercury can cause microglial activation and astrocyte death at some dose, right?

A Yes. In the Vahter study, they gave very high doses of mercury. Animals once again were fine, but when the looked at the brains, there was astrocyte death, so it might have been a threshold level to cause death of some of the astrocytes. Now, whenever you have cell death, whenever you have cell death, then the natural response in the brain is that the phagocytes, the cells that are sort of the cleanup crew cells, come along and clean up the cells debris.

That's what the glial cells do. That's glial cell activation. It's the microglia. They come

along near the phagocytes, and they come along, and they clean up the debris from the necrotic astrocytes. I don't know if that's what you're calling neuroinflammation.

Q Well, we'll look at those adult monkey studies in a minute. Let's see if we can finish going through this study while we have it in front of us. If we go to the third column of the same page, the first full paragraph, you discuss these five adult monkey studies there. I want to just go through this point briefly.

A Yes.

Q In contrast, previous studies of adult Macaca fascicularis monkeys exposed chronically to methyl mercury have indicated that demethylation of mercury occurs in the brain over a long period of time after methyl mercury exposure and that this is not a detoxification process and cites all five of those adult monkey studies, right?

A That's correct.

Q Now, in your report, although you've discussed Burbacher's infant monkey study here for several pages, you don't discuss or even reference these adult monkey studies.

A There's a very good reason for it.

Q Why is that?

A These monkey studies did not study thimerosal. They did not study ethyl mercury. If I were to embark on a total discussion of the toxicology of methyl mercury and all the papers dealing with methyl mercury, which had as we saw very different kinetics in the brain and tried to morph that into something relevant to what you get from vaccine from thimerosal, it's an undoable argument. I was talking about thimerosal.

This refers to a totally different molecule that is not in vaccines and is ill-described. It's not in vaccines, and that is given in a way that has nothing to do with the way we give it in vaccines, so of course I'm not going to start talking about that in my report. I don't think anybody wanted to hear about that in my report.

Q The adult monkey studies were focused on the adverse effects of the remaining inorganic mercury in the brains of those monkeys, and this infant monkey study's entire point I think we're going to get to is that thimerosal dumps four to five times as much inorganic mercury in the brain of infant monkeys as the equivalent dose of methyl mercury, and yet you thought that the inorganic mercury adult monkey

studies were irrelevant?

A This study under these circumstances to me provides no useful information about what happened when you administer thimerosal at the doses it's administered in vaccines. If you can show me the relevance of the study, I'd be glad to listen to it, but at this point frankly if I were rewriting my report today, I still don't think I would include this study.

SPECIAL MASTER HASTINGS: When you say "this study" --

THE WITNESS: I'm sorry. We're still talking about the Charleston and Vahter studies.

SPECIAL MASTER VOWELL: So you're not referring to the Burbacher study?

THE WITNESS: No, no, no. Of course not.

SPECIAL MASTER VOWELL: Okay.

BY MR. WILLIAMS:

Q I understand. You're saying that those adult monkey studies in your opinion are still irrelevant to the question that these Special Masters have to decide?

A I'm saying they're uninformative with regard to whether thimerosal in doses related to vaccines create any brain damage.

Q Well, are they relevant to the question of whether inorganic mercury in the brain can provoke neuroinflammation?

A I'm not even sure they're relevant to that. They're relevant to whether high doses of methyl mercury exposed on a continuous basis, very, very high doses, to monkeys that end up being behaviorally totally normal have astrocyte death and microglial activation to clean up the astrocyte death.

Q I think we understand your position. Let's see whether the authors of this paper agree with you. If we could just go down a couple more sentences? In fact, just highlight the whole middle of that third column if you would, right under where you've highlighted now. I don't want to skip anything. If you could highlight it? I think it's easier to read when it's highlighted. It says, "Results from these studies," and it's referring to the five adult monkey studies just for clarification purposes.

"Results from these studies indicated higher inorganic mercury concentrations in the brain six months after methyl mercury exposure had ended whereas organic mercury had cleared from the brain. The estimated half life of organic mercury in the brain of these adult monkeys was consistent across various

brain regions at approximately 37 days, similar to the brain half life in the present infant monkeys.

"The estimated half life of inorganic mercury in the brain in the same adult cohort varied greatly across some regions of the brain from 227 days to 540 days. In other regions, the concentration of inorganic mercury remained the same six months after exposure."

Are you suggesting that their entire discussion of this when you talked about how precious the words are in these studies, they didn't have time to put in your point that you think they had that they only did this for technical reasons the dose. They didn't choose it to mimic the program. Why would they put all this language in there if they thought this was irrelevant?

A Well, once again I don't see any of that language relevant to what happens in the brain when you give small doses of thimerosal as you would in a vaccine. This is not data you can translate from one to another. The dosing scenarios are different. The doses are huge in this study. The animals are fine anyway, so I don't understand how one in good conscience as a scientist could actually apply this data to what happens from thimerosal, from vaccines.

Q Okay. Let's continue going here because they continue discussing these adult monkey studies for quite some time. The next sentence says, "Stereologic and autometallographic studies on the brains of these adult monkeys indicated that the persistence of inorganic mercury in the brain was associated with a significant increase in the number of microglia in the brain, whereas the number of astrocytes declined."

We've already talked about that, "and that notably these effects were observed after exposure to the methyl mercury had ended when the inorganic mercury concentrations were at their highest levels, or they were also there in the animals solely exposed to inorganic mercury. In that study, they actually fed some of the adult monkeys mercury chloride just to see what would happen with that, right?

A Yes, and I think that relates to my point that you can get the damage from either.

Q Yes, and then they say, "The effects in the adult Macaques were associated with brain inorganic mercury levels approximately five times higher than those observed in the present group of infant Macaques." They obviously thought that the inorganic mercury in the brain of those adult monkeys and the

fact that it was only five times higher than what they detected in the brain of these infant monkeys was a relevant fact to put in their paper, and you don't think that's relevant?

A No. I'm saying that remember this paper is a pharmacokinetic paper, and they're talking about brain levels in this paper, and they're comparing it to brain levels in other papers. What I am talking about, and what I put in my report, and what I think is relevant is to what degree, if any, this informs you about what happens in the brain following doses associated with thimerosal-containing vaccine, and this point is not informative about that.

That's not why they wrote this paper. They didn't write the paper to answer that question, but this is what I covered in my report and in my presentation today.

Q Let's see what the next two sentences of this same paragraph are. We need to blow it up.

SPECIAL MASTER VOWELL: Also the column you're on.

MR. WILLIAMS: Just right under where we've been. I'm sorry. Page 6, right-hand column. It's the last two sentences in the last full paragraph on the page.

(Discussion held off the record.)

BY MR. WILLIAMS:

Q Okay. The last two sentences. Let me read them. It says, "In addition, whether similar effects are observed at lower levels in the developing brain is not known." They obviously thought that the developing brain could be different than the adult monkey brain.

A They said they didn't know.

Q And then they say, "It is important to note than an active neuroinflammatory process has been demonstrated in brains of autistic patients, including a marked activation of microglia," and they cite the Vargas paper from 2005. Now, do you believe that these points they're making are just irrelevant?

A Irrelevant to what question?

Q Whether thimerosal can cause autism.

A They're totally irrelevant to whether thimerosal can cause autism, and I'll tell you why. Number one, the Vahter paper animals despite the high doses they got, despite the continuous dosing, the higher levels of methyl mercury in their brain, did not have any behavioral abnormalities, did not show any abnormalities. They showed that there was so much mercury in the brain that it was toxic to astrocytes,

and so that the microglia were activated to clean up the astrocytes. How that relates to doses in vaccines causing autism completely escapes me.

Q Well, what if as these authors suggest the developing brain could be more sensitive than the adult brain to the neuroinflammatory process and we only have a difference of five times. We're not even in order of magnitude different here, right?

A Yes, but that can't be playing a role. It's impossible for it to be playing a role because as we saw if you look at the population in the Seychelles, and you look at the population in the Faroe Islands, they have far more mercury in their brain, and they have it from birth. They have it from birth. They're cord blood levels are five to 10 times what it is in the United States. Yet, they don't have autism. They don't have an increased rate of autism.

Q I'm going to interrupt this discussion of infant monkey brains and adult monkey brains for a minute and go to this Faroe Island study that you flashed on the screen.

A Okay.

Q If we could first show the front page.

SPECIAL MASTER VOWELL: Why don't you give us the reference number, Mr. Williams?

MR. WILLIAMS: This is Reference Master List 130. It's a DOJ exhibit.

MR. WILLIAMS:

Q This is the study you showed, right?

A That's correct.

Q Now, what you didn't show, what you didn't bring out was in the discussion section of this paper on page 6 of this exhibit, the authors say, "There are at least two partly conflicting reasons why such a conclusion might be regarded as skepticism," and the conclusion they're talking about is the fact that the rate of autism in the Faroe Island population seems to be the same as the rest of the world, okay?

One of the possibilities they discuss is that the number of possible susceptibility genes would probably be very much lower in a genetic isolate such as the Faroe Islands where the population pretty much in breeds with each other, right? The Faroe Islands is not a good genetic model of the rest of the world, correct?

A Well, it is what it is. It's a population with dramatically higher amounts of mercury in the brain, and they studied that population. Is that population necessarily applicable to every other country in the world? Possibly yes, possibly no. I

mean, they haven't shown it's not. They're raising the possibility.

It also should be noted however that the same patter was observed in the Seychelles, and there does not appear to be any increased rate of autism despite the very high levels of brain mercury in the individuals in the Seychelles. Now you can say well, maybe they also don't have the genetic susceptibility, but nevertheless I think there's a pattern here.

It doesn't actually prove it, but I think there's a patter here that is very highly suggesting that the amount of brain mercury does not determine autism.

Q Then let's go to the top of the next column where I've highlighted that. They say this genetic isolation would then lead to a much lower rate of autism in the Faroe Island and in other regions where the autism gene pool would be larger.

A They're leaving that possibility open, yes.

Q Right. Now, why didn't you bring that out on direct?

A Because for every paper I talked about and in fact anybody participating in these hearings, if they went and talked about every bit of author speculation in every one of the papers, these would be

very, very, very long hearings. This is not a major conclusion of the paper. This is author speculation.

I simply pointed out the major conclusion of the paper is that in the Faroe Island despite the very high levels of brain mercury, there is no increased rate in autism, similar to the fact that in the Seychelles despite the very high levels of mercury in the brain, there is no increased rate of autism.

Now, in any studies that I've talked about, we could go back, and we could pick up all kinds of speculation of the authors as authors are supposed to do in studies in terms of indicating the limitations of the interpretation of the data, but that's the speculative part in the discussion of the paper.

Q Let's see if they list another reason why this study probably underestimates the true autism rate in the Faroe Islands. Let's go to the next highlight. They're saying here the fact that the rate is different could actually mask underlying major differences across populations rather than itself being supportive of any unifying theory for autism etiology, correct?

A Theoretical possibility.

Q In both the Seychelles and in the Faroe Islands, the mothers and eventually the children eat

an enormous amount of fish compared to the rest of us, right?

A Absolutely they do.

Q And isn't fish very good for brains, so that even if the mercury was having an adverse effect on their brains, the fish could counteract them?

A The same thing in the United States. In the United States we eat a fair amount of fish compared to some other populations, and yes, there is data that it's good or neurodevelopmental function. There is no data, not one bit of data that I'm aware of, that fish eating protects against autism.

Q Let's go to the next highlight please in the same study. It says, "The high male to female ratio..." They had what? Six males to one female, right? "The high male to female ratio suggests that some girls with autism spectrum disorders may have been missed." Let's go to the next highlight. "It is likely that some girls with autism in this population may have remained undetected in spite of the rather meticulous screening of the Faroe Islands schools performed," correct?

A It's always possible, and that may actually explain why their rate of autism was less than, for example, what we see in the United States.

Q Nevertheless, the authors of this paper have pointed out two significant reasons why this could well be an underestimate of the true rate of autism there.

A Sure. It's within the range of possibilities.

Q All right. Let's go back to the monkey study. Just a few more points from the Burbacher study now going to the last page. We could blow that up. They discuss the IOM report They say that a recently published second review of the IOM in 2004 appears to have abandoned the earlier recommendation to do more studies on thimerosal as well as backed away from the American Academy of Pediatrics' goal to remove thimerosal from vaccines, right?

A Correct.

Q That is what the IOM committee in 2004 said, right?

A What is what the IOM in 2004 said?

Q It said shouldn't do any more studies on thimerosal and autism.

A Right. Correct.

Q And you shouldn't worry about the fact that thimerosal is still in some infant vaccines in this country and other places around the world.

A Right. That was the IOM's conclusion.

Q And Dr. Goodman was on that committee, and I think we're going to see him Friday afternoon, so I don't want to debate that with you other than to say, and I want to read this next sentence and then ask you about it, the authors of this paper, Dr. Clarkson included, say, "This approach is difficult to understand given our current limited knowledge of the toxicokinetics and developmental neurotoxicity of thimerosal, a compound that has been and will continue to be injected in millions of newborn infants."

Now, do you still think the IOM's 2004 recommendation is a good one?

A Well, look. I mean, you have to take cognisance of the fact that since 2004, continuing bodies of epidemiologic studies has come out to reaffirm the IOM's conclusion. The data has come out that has shown that we take thimerosal away from vaccine, the rate of autism continues to rise unabated.

Your own epidemiologist testified that the epidemiologic data effectively rules out an association between thimerosal-containing vaccines and autism in general, so yes, based on all that I do strongly support the 2004 IOM recommendation. IOM can

always go back and revisit its recommendations. It hasn't done that. It hasn't even talked about doing that to my knowledge.

Q Most of those other agencies, if not all of them you've listed in one of your concluding slides. They basically all just cite the OIM report for their own conclusions, don't they?

A No. I don't think you can say that. I don't think the World Health Organization and the Centers for Disease Control, the American Academy of Pediatrics, American College of Medical Toxicologists, the European Medicines Agency all simply defer to the IOM. I don't think you can do that. Yes, they may cite the IOM, but I think it is an incorrect conclusion to say they're simply repeating what the IOM said and adopting without due intellectual consideration the IOM conclusion.

Q Do you know whether any of those organizations have discussed in their analysis this infant monkey study or the implications of the Vargas paper for neuroinflammation as the cause of autism?

A The Vargas paper deals with methyl mercury. I mentioned a whole multitude of reasons, and if you want, I'll go over them again, although we've talked about them a number of times of why the Vargas paper

probably is not informative about thimerosal-containing vaccines and autism.

Q Sorry. The question is do you know whether any of those organizations' analyses have considered the Burbacher infant/monkey study data and the implications for the Vargas neuroinflammatory process that was discovered in 2005?

A And my answer to that is I would have to go back and look to see whether they did. Frankly, I doubt that they did because the Burbacher study supports the conclusion and the other data I think is not informative about the conclusion.

Q The last highlight on this paper is the very next paragraph, the final paragraph. "The key findings of the present study are the differences in the disposition kinetics and demethylation rates of thimerosal and methyl mercury. Consequently methyl mercury is not a suitable reference for risk assessment from exposure to thimerosal-derived mercury."

Then they say, "Knowledge of the biotransformation of thimerosal, the chemical identity of the mercury-containing species in the blood and brain and the neurotoxic potential of intact thimerosal and its various biotransformation products,

including ethyl mercury, is urgently needed." Now, do you agree that studies on these questions are urgently needed, or do you still agree with the IOM 2004 that we don't need to do any study?

A Well, I can only reiterate what I said before, that since the IOM 2004, the epidemiological data has become so much stronger suggesting that there's no link that there would be no reason to go back and requestion the 2004 IOM conclusion.

Q I'm sorry. Are you finished?

A Yes.

Q Okay. Are you aware of any epidemiological studies on regressive autism and thimerosal?

A No.

Q Even one?

A No.

Q And yet you think the door is closed, and there's no reason to look at that?

A No. I was talking about autism in general. I was talking about autism in general. Now, to what extent the information can be related to epidemiological studies regarding regression, I would leave that to the epidemiologist who is going to be testifying here.

Q By the way, I think you said on direct that

you acknowledge that there's a difference in gender responses to mercury?

A No. I was talking about the Adams tooth study, and I said that they used many more males in the ASD group than in the control group and that may have potentially influenced the results. We don't know if it would have or not. At least it's something that probably should have been controlled for.

Q Well, let me just ask you now, and it may save me a little cross later, do you agree that male human boys will excrete mercury more slowly than girls?

A There is some limited data mostly related to inorganic that that might be the case.

Q What was the sex breakdown in this infant monkey study? Where these all male infant monkeys, or were there female infant monkeys mixed in here?

A I don't recall. I'd be glad to look if you like.

Q Well, I can tell you it was roughly half and half.

A Okay.

Q Wouldn't that also have the same problem as the tooth study? If males tend to retain more mercury than girls, wouldn't you expect that to be true in

primates as well as humans?

A Well, you said there was half and half. That was not the case in the tooth study.

Q They don't report any gender differences in this study, but if males retain mercury more than girls, wouldn't a fair inference of this study be that the male monkeys could well be the ones that had higher levels than the female infant monkeys?

A Well, I think that's quite speculative. You can speculate maybe that was the case. Maybe it wasn't, but even so, if you look at the levels of mercury in the brain, they're quite low, so yes, they're a little bit higher in the males. Even if your speculation were true, it would not materially affect the results.

Q Okay. Now I'm going to go through the adult monkey study. We're going to do it more briskly that we've gone through this one, but there are a few points I want to discuss with you about this study.

A Sure.

Q Did you read those studies before you wrote your report, or did you read them after you found out that we thought they were relevant?

A I read them when they came out. I read them when they came out.

Q Okay. If we could start with our Exhibit 64 --

A Would it be too much trouble to ask if I could have a copy of that in front of me?

Q You bet.

(Discussion held off the record.)

MR. WILLIAMS: This will save time later even though it's taking a little time now.

SPECIAL MASTER VOWELL: Not a problem.

THE WITNESS: Thank you very much.

BY MR. WILLIAMS:

Q I do want to go back. I forgot one point about that infant monkey study that I needed to make just to finish up with it. If you go to page 5 of Burbacher infant monkey study in the right-hand column, I forgot to just nail down the amount of inorganic mercury in the brain of the thimerosal-exposed monkeys. It's about three sentences up from the word "discussion." Just blow the highlight up to show it.

They said, "The average concentration of inorganic mercury did not change across the 28 days and was approximately 16 nanograms per milliliter, and you said it was about 10.

A No. I said it was a little over 10. If you

look at the figure, you see you have to sort of estimate it. I said it was a bit over 10. They obviously knew the number. If you look at the figure, you can see it's pretty hard to tell whether it's 12 or 14.

Q Right. But they're reporting their data here, not just guessing, right?

A They actually had the actual number. I was talking from the graph.

Q Right. Now, this is just the average level, right? There's some of these monkey had higher levels than that just as your bell curve would predict?

A Probably, yes.

Q And if they had a lot more monkeys, they would have some that would be even higher on the spectrum, right?

A Probably most would fall at about two standard deviations from the mean.

Q And you had conceded just a few moments ago that because they were unable to detect the inorganic mercury and the methyl mercury in a lot of methyl mercury monkeys, a fair estimate of the average level of the inorganic mercury in the methyl treated monkeys was four to five?

A I don't know what the number was. I think I

said it might be closer to seven, but if you want to use four to five, I'll take four to five.

Q You might have even said three. My point is --

A No. I said down the region of three is what you would expect if they were actually given the doses that you would give in a thimerosal-containing vaccine.

Q But isn't the take away message from this study that 20 micrograms of ethyl mercury when injected into the infant monkeys resulted in an average of 16 nanograms per milliliter whereas 20 micrograms of methyl mercury ingested by those infant monkeys only resulted in four or five nanograms per milliliter of inorganic mercury in the brain?

A No, no. That was inorganic mercury at the 28-day time point, but there was still 10 times as much methyl mercury that remained in the brain at the end of that point. You showed me before this language about the demethylation of methyl mercury over time to inorganic mercury, so there was this very large store of methyl mercury that was still there that would undergo demethylation to inorganic mercury.

Q Wouldn't 90 percent of it at least be eliminated? They said only 10 percent was converted

to inorganic mercury?

A No. No, because as I mentioned, there was no statistical difference between the methyl mercury level at the first day they started looking at brains and at the find day they started looking at brains, so clearly if that methyl mercury was going any place, it was leaving the brain. It was leaving the brain so slowly it could not be detected, so most of it was going to be demethylated to inorganic mercury.

You'd end up with a much bigger inorganic mercury load, which is exactly why when you look at the Seychelles' very high level of mercury in the brain, it's from methyl mercury, and they are a fish-eating population, and that's their source of mercury.

Q The Seychelles studies didn't speciate the mercury. They just measured total mercury.

A Total mercury.

Q Right.

A But I think it's fair to say it's all from methyl mercury in the Seychelles.

Q Are you talking about the dead infant study?

A The brain mercury, yes.

Q There wouldn't be time for the methyl mercury to have demethylated in the infants that were one or two days old.

A Well, no, but they are getting exposed even from the pre-natal time period.

Q Well, no. Let's go now to the adult monkey studies. The first is Exhibit 64. I want to first just do an overview of the study design so we have that in our minds.

A Please.

Q Table 1. First of all, I'm sorry. Let's show the title and the authors here. Dr. Burbacher was the senior investigator on this study, correct?

A Probably. His name was last, yes.

Q And the people he's working with there, some of them are from the Karolinska Institute in Sweden?

A Yes.

Q And the others are at the University of Washington, right?

A Correct.

Q If we go now to Table 1, I think it will show us the design of this adult monkey study. I don't know what page. I'll look.

SPECIAL MASTER VOWELL: It's going to be page 2.

MR. WILLIAMS: I'm sorry. That's not the design of the study I believe. Well, it will give us some hint at the design if we go to Table 1. Let's do

that.

(Discussion held off the record.)

MR. WILLIAMS: What paper are you in? That is the design I wanted to show. I just want to make sure we've got the right study here.

BY MR. WILLIAMS:

Q Have you found that table in your papers, the one we just had on the screen?

A Table 1?

Q Yes.

A Yes, I have Table 1.

Q And which exhibit number is that in?

A PMR 64.

Q Okay. I've got it now. This is Exhibit 64, page 2, Table 1, and what they had was they had five adult monkeys who got methyl mercury for six months, correct?

A Right.

Q You see those are the monkey numbers down the left-hand column.

A Right. Yes, that's correct.

Q And then five adult monkeys who got methyl mercury for 12 months?

A Correct.

Q And then five adult monkeys who got methyl

mercury for 18 months?

A Correct.

Q And then they have five to whom they gave methyl mercury for 12 months and then went six months with no exposure.

A Correct.

Q And they had four controls with no exposure.

A Correct.

Q And then they had three monkeys that they fed mercury chloride to for three months.

A Correct.

Q Okay. So that was the general design of the study. By the way, all five of these papers report results of the same study. I mean, it's just different things they looked at, but it was the same study on these same monkeys.

A I believe so.

Q Okay. So now if we go to Exhibit 32, and this is another one of these five studies, and we'll show the title quickly so we have it for the record, the Autometallographic Determination of Inorganic Mercury Distribution in the Cortex.

A That's the cortex of the calcarine silvers.

Q Right. If we go now to the second page of this study, at the top right-hand column. Just blow

that up if you would. It's referring to a figure, but the copies we have don't allow us to look at those, and you're probably not any more qualified than I am to say what they mean pathologically, are you?

A Maybe a little.

Q Okay. The way they were detecting the inorganic mercury was using the silver technique so that it would show up in the microscope, right?

A Correct.

Q Okay. It says the control section is virtually free of silver grains.

A Can you show me where you're reading, please?

Q Yes. It's the --

A I got it. Okay.

Q It's like the second sentence of that paragraph. Yes, it's highlighted now. The control section is virtually free of silver grains. The few bright spots in the control section actually represent capillaries and blood vessels cut in or near cross-sections, so in the controls, they really didn't detect any inorganic mercury, correct?

A Based on their limited detection. Certainly, there was some inorganic mercury there, but it was relatively low compared to their limited

detection.

Q That's right. And then they go on to say the six-month methyl mercury exposed animal has significant silver grains distributed across all layers of the cortex.

A Right.

Q Do you see that?

A Referring to the calcarine in the cortex.

Q Yes. And then it says a similar distribution across all cortical layers is present in the 12- and 18-month exposure groups and in the clearance group. That's the 12 on, six off group, so that the inorganic mercury they were detecting in the brains of these monkeys at least in this section of the cortex they looked at was spread across all layers in all groups, correct?

A Correct.

Q The next paragraph, if we highlight that, the astrocytes and microglia appear to accumulate high concentrations of mercury relative to all other cell types, and then they go on to say that moderate mercury deposits are detected within these cell types in the six-month group, and then these cells sequentially become more heavily labeled with longer exposure duration, so what they found was that the

inorganic mercury did build up in all these layers of the cortex over time in these monkeys.

A Yes. They continued to feed them, and it continued to build up, yes.

Q And then at the bottom of that paragraph, it says, and this is the last sentence, "Some of these individual cells in the 12- and 18-month methyl mercury exposed group were so heavily labeled as to completely obscure the nucleus associated with that cell," do you see that?

A Right. Right.

Q Then the next to last sentence on that page, in the same column, they talk about the labeled neuron, and although they found that most of the inorganic mercury was in the microglia and the astrocytes, it says here that labeled neurons in the 18-month group were calm, so they found the inorganic mercury even in the neurons of these adult monkey brains, correct?

A Sure.

Q And it says, "These grains, although relatively small compared to those found in the astrocytes and microglia were readily visible with brightfield optics." That's talking in the neurons.

A Correct.

Q Now, is inorganic mercury inside a neuron, is that a good thing or a bad thing?

A Most of the time you won't see very much in the neurons. They're more in the astrocytes and glia, but you have to understand that the design of this study was such that you might expect to see them in the neurons because they gave 50 micrograms per kilo per day, which is equivalent in a 70 kilogram person. That's 3,500 micrograms a day of methyl mercury. Now, if you remember, the average diet of methyl mercury in the United States is about 11,000 micrograms a year.

Here, they were given 3,500 micrograms a day, so when you give that astronomical amount of mercury, you're certainly going to expect to see some mercury in the neurons of the brain.

Q If we look at the figure on page 4 and the caption to that figure, and this is still in Exhibit 32, and this is page 4 of Exhibit 32. I just want to reiterate the last sentence of that figure. It says, "All neurons contain several silver grains within their cell bodies, correct?

A Are you looking at Figure 4?

Q Figure 2.

A Figure 2. I'm sorry.

Q Figure 2. I'm sorry. On page 4.

A All right.
Q The last sentence.
A Right. Right.
Q Right. Okay. Now, if we go to the very next page, the top of the first column right there it says, "The level of the silver staying within the inorganic mercury exposed animals was much lower than that observed in the methyl mercury-exposed," and by inorganic mercury exposed, they're talking about the mercury chloride animals, right?
A That's correct.
Q And it was much lower, which is what you would expect, right? Because the gut is not going to absorb inorganic mercury as efficiently as it does methyl mercury, right?
A Right. It won't cross the blood-brain barrier as well.
Q And then inorganic mercury is not nearly as readily able to cross the blood-brain barrier as methyl mercury, right?
A That's correct, and I just want to take a look at the doses also that they use of the mercuric chloride, if I could do that?
Q Sure. I was trying to establish the background here that as expected, the animals fed the

inorganic mercury had a lot lower levels in their brain than the animals fed methyl mercury.

A Right.

Q And then nevertheless if we go to the next column, the last sentence before the word "discussion," just above "discussion," the last sentence says, "It is also important to note that the inorganic mercury exposed group had virtually no methyl mercury present, yet this group still experienced a significant increase in cell number as well as detectable staining of mercury deposits within the astrocytes and microglia," right?

A Right.

Q So even this very low level of inorganic mercury from the inorganic mercury-exposed monkeys was enough to cause these astrocytes and microglia to react to it.

A If you look, it really wasn't a very low level of inorganic mercury. If you go to their infusion protocol for the inorganic mercury, and I just had it here. Let me see if I can bring it up again. If you take a look, and this is on Exhibit 60. It doesn't say whose Exhibit 60. It says 60 on it. The speciation of mercury in the primates blood paper with Vahter as the first author, on page 222, it gives

the infusion protocol and explains that and explains why.

In talking about mercury chloride, the infusion rate was 200 micrograms per kilogram for body weight per day, which was expected based on the results of the pilot studies. You get blood mercury concentrations similar to the methyl mercury in monkeys.

Q Okay. Let's turn the page and look at Table 1 here to see what amounts ended up in their brains.

SPECIAL MASTER VOWELL: We're on which exhibit?

MR. WILLIAMS: This is Exhibit 32, page 6 now, Table 1. Pull up Table 1.

BY MR. WILLIAMS:

Q The inorganic exposed-monkey is the last line in this table. Do you see that?

A Right.

Q And the amount of inorganic mercury detected in this part of the brain that they looked at in this paper was .106 micrograms per gram, right?

A Right, which I pointed out parts per million as opposed to the parts per billion that you would typically expect to see.

Q Exactly, so that if we were to convert this

to nanograms, we would have to multiply that by a 1,000, right?

A Correct.

Q And we would have 106 nanograms. To convert this to the type of measure we were looking at in the infant monkey study, we would make that 106, right?

A Right.

Q Now, what's the standard deviation here for this particular number?

A 0.042.

Q And again you'd have to multiply that by a 1,000 if you're going to do an equivalent calculation, so the standard error would be 42 nanograms per milliliter.

A Okay.

Q And the standard error as you said I think on direct represents in your bell curve the middle 95 percent of the population?

A I was talking about standard deviation.

Q What?

A I was talking about standard deviation, not standard error. They're different parameters.

Q Even if you treat this as a single-standard error, if you subtract 42 from 106, what do you get down to? 64?

A Okay.
Q And in the infant monkeys we had an average of 16, so now we're only seeing what? A three- to four-fold difference in level?
A Of inorganic mercury?
Q Yes.
A That doesn't consider the methyl mercury that was also present, which was potentially higher.
Q The inorganic --
A That's correct.
Q Right. And yet it was still enough to set off activation of astroglia and microcytes, wasn't it in the adults?
A Well, in the adults. Remember, this is inorganic. There is also a significant load of organic, and in the infants, there was a much greater load of organic mercury as well that also had to be taken into consideration.
Q Right. Now, you were saying that this .042 was a standard error, but just below that in the caption of this figure, this table, it says, "The values in parentheses represent the standard deviation."
A No, no. You said standard error. You said standard error.

Q Okay. Well, let's make sure we're straight here.

A Okay.

Q It says, "The values in parentheses represent the standard deviation."

A That's correct.

Q Isn't that right?

A That's correct.

Q So back to your bell curve, using standard deviations, you go two standard deviations from the middle in each direction, right?

A Correct.

Q And the idea is that statistically that captures 95 percent of the population?

A That's correct.

Q And you have the two and a half percent at one end and two and a half percent at the other end?

A That's right.

Q Okay. So if we go now to the bottom of the bell curve of this inorganic measure here, and we subtract 84 from 106, we get down to 22 nanograms per milliliter, correct?

A Okay.

Q Almost the same as the inorganic mercury levels in the infant monkeys.

A Okay.

Q So statistically isn't it fair to say that the results of the infant monkey studies, they're not really statistically different from the results in these inorganic mercury-exposed monkeys in terms of the level of inorganic mercury detectible in the brain?

A No. They're totally different. I don't see how you can say that. You are talking about virtually the lowest possible level in this study, far below the average level, far below the higher level.

You are just taking the lowest possible level in this study, and you are saying that is somehow equivalent to the average level that you may see in the infant monkeys only looking at the inorganic mercury forgetting once again that even doing that, you are ignoring the fact that there's still 10-fold higher methyl mercury in the infant monkey. No, there's a vast difference in the mercury concentration.

Q I'm only going to be talking about inorganic mercury here, so the fact that you keep wanting to talk about methyl mercury levels, which we are know are changing in these adult monkeys, and in fact at 18 months the methyl mercury was almost all gone from the

brains of these adults right?

A Right.

Q So let's concentrate on inorganic mercury here for a moment.

A Sure.

Q The bell curve for these inorganic mercury-exposed adults with this standard deviation would go down to 82 below 106, which is 24, right? Do you know what the standard deviation was for the measurements in the infant monkeys?

A We can look it up if you have the Burbacher paper handy.

Q I don't think it's in there.

A Well, then I can't tell you.

Q I looked for it, and I couldn't find it.

A I'll take your word for it.

Q But you agree there would be some, right?

A Sure.

Q So those confidence intervals between this inorganic mercury level in the adults and the inorganic mercury in the infants, they would overlap significantly, wouldn't they?

A Well, they didn't report confidence intervals. They reported standard deviations, and there's a difference, but if you're saying that in the

adult monkeys, just looking at the inorganic mercury, if you take the very, very lowest level of inorganic mercury in the brain, this particular part of the brain, and you compare them with what is perhaps the higher levels in the Burbacher study, sure, there's a possibility of some overlap.

Q Okay. And so statistically, they're not really different.

A No. You can't say that. You can certainly have overlapping values that are statistically significantly different. If you look at the means, they're vastly different. If you look at the standard deviations, they're not that wide. You will definitely be able to anticipate that they would be statistically significantly different. I don't know.

I didn't do the calculation, but just because the very, very bottom level of one number may overlap with the upper level of another value does not mean that they're not statistically significantly different.

Q In the adult monkeys, isn't it true that they found microglial activation and astrocyte activation in every monkey?

A They found astrocyte death and microglial activation, and the microglial activation is a normal

response to astrocyte death.

Q They found it though my point is in every monkey, even the ones that had the lowest levels. In other words, there was no threshold level of inorganic mercury that would have not provoked microglial activation.

A Can you show me where it says that?

Q In this study.

A Can you show me where it says that the ones that even with the lowest level had astrocyte death and microglial activation?

Q Well, they report microglial activation in all the monkeys.

A They say every single one of them had it?

Q Well, I don't know if they actually say it somewhere. I mean, you might have to literally look at every word of every paper.

A Are you assuming that?

Q They don't report any threshold value here below which there was no activation, do you agree with that?

A I don't remember indicating that one way or another. I mean, I don't think you can assume that the monkeys that had the lowest level of inorganic mercury had this effect. It seems to be --

Q Well, they do report that the monkeys that had the lowest level of inorganic mercury were the ones to whom they had said inorganic mercury, and yet in those monkeys, they still detected microglial activation.

A Yes, with an average level up in the almost parts per billion range, not parts per million range. By the way, I think your question said astrocyte activation. It's astrocyte death.

Q Okay. Well, let's keep going through this, and maybe that will get clarified a little bit. If we stay with Exhibit 32 and go to the next page, which is page 7 of the exhibit. It's page 331 of the study. It's the first full paragraph where it says, "We have concluded..." The right-hand column, the first full paragraph it says, "We have concluded that the microglia in our study represent a form of activated microglial cells," correct?

A Correct. As I said before, the microglia become activated as phagocytes because of the astrocyte death.

Q Well, but they say it also may be as a result of the mercury right below that. If you look, it says, "These activated microglia may be a transient microglia form in our case relating to the presence of

mercury or damaged astrocytes," right?

A Right. However, you will always see microglia activation if you have astrocyte toxicity.

Q Now let's go to the very last two sentences of this paper on page 8 of Exhibit 32. It says, "The lack of methyl mercury exposure in the inorganic-exposed tissue and low levels of methyl mercury in the clearance group indicates that the inorganic mercury is associated with the observed increase in microglia in all mercury exposure groups." The microglia increased 165 percent in the inorganic exposed monkey group, correct?

A Correct, to the response of astrocyte death.

Q Now let's turn to one of the Charleston papers, Exhibit 116. You should have the exhibit numbers at the bottom of your studies, Doctor.

A I do.

Q That's the title of the paper, Changes in the Number of Astrocytes and Microglia in the Thalamus, and then I just want to go to the bottom of this abstract and show you what the conclusion of this was in the abstract of the paper. "The data suggests that inorganic mercury present in the brains, accumulating after long-term subclinical methyl mercury exposure may be approximate toxic form of

mercury responsible for the changes within the astrocyte and microglial populations."

Now, do you agree with them that this is a neurotoxic result?

A Well, there's the astrocyte toxicity, so by definition it's a neurotoxic result. Remember however that we don't know if it has any clinical significant because the monkeys were all clinically normal and that the doses that were used was far, far in excess of anything that any reasonable human would ever be exposed to.

Q They discussed the microglia, the effect of the activated microglia on page -- my page numbers are blanked out. It's page 134 of the study. I can't read the exhibit page numbers on this. At the very bottom on the section on microglia, and I think we've got it prehighlighted there, the bottom of the section on microglia, the left-hand column, "An increase in microglia may have detrimental consequences to the central nervous system during recovery from a toxic episode because it has been suggested that activated microglia may interfere with neuronal recovery after injuries. Is that true?

A If they say it, I'll accept it.

Q Okay.

A But you want to ask a neurologist about that or a neuroscientist.

MR. WILLIAMS: I know that it's getting late, and I definitely have probably an hour to go at least.

SPECIAL MASTER VOWELL: Then I think it would be appropriate to take our lunch recess now and we'll return in an hour, and by my watch, that would have us coming back at 2:15.

MR. WILLIAMS: That would be fine.

SPECIAL MASTER VOWELL: Okay. We're in recess.

(Whereupon, at 1:15 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 2:15 p.m. this same day, Monday, May 19, 2008.)

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

(2:20 p.m.)

SPECIAL MASTER VOWELL: We're back on the record. Dr. Brent remains on the witness stand, and he's aware that he's still under oath.

Whereupon,

JEFFREY BRENT

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

SPECIAL MASTER VOWELL: You may proceed anew, Mr. Williams.

MR. WILLIAMS: Thank you.

CROSS-EXAMINATION (RESUMED)

BY MR. WILLIAMS:

Q Dr. Brent, just a few more questions on the adult monkey study, and in fact just on one of them, Exhibit 116, which is the Changes in the Number of Astrocytes paper.

A Yes.

Q You several times described this group of studies as a high-dose methyl mercury study. If we start on the second page of this paper, in the left-hand column, in the first full paragraph. When they say, "The above examples," there's a long list of

citations of the previous studies on monkeys.

A Right.

Q Where neurotoxicity had been demonstrated in the brain, and what they say here is, "The above examples of methyl mercury induced damage in the primate brain have been demonstrated following relatively high doses of methyl mercury exposure, and these exposures usually result in the development of behavioral symptoms. In general, subclinical levels of methyl mercury exposure have not received as much attention in experimental models."

This is particularly true for research carried out in primates. What I want to ask you is don't you agree that the whole design of this study that resulted in these five papers was to test the lowest dose yet on adult monkeys?

A I don't know what their motivation is to doing the study, but let me comment on these points. They were looking at a model that they describe that they wanted to be subclinical. In other words, without any clinical effects, or if so, they were minor clinical effects, and that's what they achieved in this study. These monkeys were behaviorally fine.

They did not have any clinical abnormalities that anybody could see, but nevertheless the dose that

they used was 50 micrograms per kilogram of body weight per day. That translated into a 70 kilogram person of 3,500 micrograms a day remembering that for the general population our yearly intake of methyl mercury is about 11,000 micrograms, so in three days, these animals had what the average person would have in a year, and they just did it continuously.

Yes, it was subclinical in the sense that there were no effects observed, but certainly the doses used in these studies bear no relevance whatsoever to the doses used, for example, in the thimerosal-containing vaccine and in fact bear no relevance whatsoever to the amount of methyl mercury that we all get from our normal fish eating and chicken eating every day. That's why I called it a high-dose study.

Q Then on page 135, which again I can't see the exhibit page, but it's the next to last page of text of the study. I'll tell you the exhibit page when we find it.

MR. WILLIAMS: What page of the exhibit is it? Page 9 of Exhibit 116 in the right-hand column, about three sentences up from the bottom in the middle of what you have highlighted there.

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BY MR. WILLIAMS:

Q They characterize this. They say, "The continued accumulation of inorganic mercury over time within the brain following chronic low level exposure to methyl mercury may prove to be the proximate toxic form associated with this type of exposure scenario," so at least these investigators were characterizing this as a low-dose study. I know you disagree with the way they characterize it.

A Mr. Williams, would you like me to testify that 3,500 micrograms a day of methyl mercury is a low-dose exposure? I cannot do that.

Q Now if we go to again in this same study the previous page, which then is page 134 of the study in the left-hand column, just above the word "microglia." It's in bold there. It says, "The widespread loss of astrocyte can be expected to disrupt the compositability of the astrocytes to carry out their supporting function for neurons, and ultimately their loss would be expected to impact the overall function of the central nervous system.

"However, at the exposure dose and duration they used in this study, the loss of astrocytes has not resulted in the loss of neurons within the thalamus." Do you agree that eventually widespread

loss of astrocytes could affect neuronal function?

A Well, I think if you gave so much mercury or so much of any other potential substance, that can affect astrocytes obviously much more than they gave in this study. You can ultimately get to the point where you would cause some neurotoxicity. I think that's the basic principal of dose response. You can certainly get there if you give enough.

However, I should point out there really wasn't much loss of astrocytes, so they're just talking about what might happen if the doses were even greater to the point where you might see that. Once again, we're in the discussion and the speculative part of the paper. This is not the data from the paper.

Q Now if you'll turn back to page 135, the page we were on originally, on the left-hand column, just under where it says, "Potential toxic role of inorganic mercury..." Yes, that's what I want. It says, "The microglia population is a responsive cell type. Once damage has been repaired following activation after injury, microglia are known to return to a quiescent sate. However, the number of activated microglia remained elevated..."

Then we go to the next column "...in the

monkeys of the clearance group, which were kept unexposed for six months following 12 months of methyl mercury exposure. This group had very low concentrations of methyl mercury, but retained elevated concentrations of inorganic mercury at levels comparable to the 12-month exposure group."

This suggested inorganic mercury may be the proximate species of mercury responsible for microglia activation, a situation similar to that posed for the cortex study we already looked at. Now, do you agree that normally microglia, they have a protective role. They come in. They clean up whatever is there, and then they return to their quiescent state?

A To the extent that I understand microglia, which is limited, I would say yes.

Q Okay. And if they stay activated, then they can become toxic to neurons or astrocytes?

A Well, once again my understanding of microglia is more limited than other people who are going to be testifying later, so I'm going to have to limit the scope of my answer here. My understanding is that microglial activation is not necessarily a bad thing and that the effects here are not necessarily indicative of any neuropathology, but once again remember we're talking about inorganic mercury effects

at the concentrations that they give here.

If the inorganic mercury is causing adverse effects, then if the seafood and the chicken people are eating, and not the vaccine, because that's where the far greater exposure comes from, and that doesn't make any sense because everybody eating seafood and chicken, including children who are getting it via breast milk, getting the methyl mercury by breast milk, and we don't think of breast milk as a neurotoxin.

Q If we go down the column on the same page to about where you have it highlighted where it says, "Further loss of astrocytes..." It says, "Further loss of astrocytes would be expected to have deleterious effects on the neuron population, for example, through an excitotoxic mechanism." You were here when Dr. Kinsbourne testified that was his --

A Hypothesis.

Q His understanding of the mechanism that could likely be at work here, that you would have astrocytes no longer able to take up glutamate, so you have an excess of glutamate and have neurons get overexcited, right?

A Well, once again, you're getting little out of the mercury area, so my answer here is going to be

quite limited. What I took away from Dr. Kinsbourne's testimony was that he was hypothesizing that there was excitoxic mechanism related to astrocytes' effect, but here, for example, in this study there really wasn't even that much loss of astrocytes and certainly what we talked about, the exposure scenario. I won't bring that up again.

Q Right. Although you want to talk about the methyl mercury dose here, you recall that the authors of the infant monkey study made a point of saying that the levels of inorganic mercury in the brains of these adult monkeys was only five times higher on average than the levels they found in those infant monkey brains, right?

A That's right, and I think that's very good evidence therefore that the inorganic mercury is not acting as a neurotoxin or else we're being poisoned every day, and we're having autism being formed every day from breast milk, from seafood, from chicken.

Q And then a sentence we haven't read yet, it's just after it says Exposure Scenario, I read that one. It says, "This form of long-term toxic response may be mechanistically different than the focal damage associated with acute high-levels exposure to methyl mercury." Do you understand? In other words, in

classic methyl mercury high dose toxicity, you get lesions in particular parts of the brain, don't you?

A You do.

Q Some of those are probably from edema causing extra pressure, and the fissures fold, and you get focal damage in the fissures of the brain, right?

A Well, there's lots of different reasons.

Q But here what they saw was microglial activation in all parts of the brain they looked at, a global event.

A Where do you see that global?

Q Well, I'm just asking you the studies in general. They report on --

A But they looked at very specific parts of the brain. They looked at thalamus. They looked at calcarine cortex, which is part of the visual pathway, which is one that is particularly sensitive to mercury toxicity.

Q And then a final point from this paper if we go back to page 133. Well, let's see, three pages prior to what we were just looking at. Okay. It's a section on the left-hand column under neurons and oligodendrocytes. I want to read starting at the third sentence of that paragraph, above that. The third sentence of that paragraph starts, "The lack of

change...".

The authors of this study say, "The lack of change, increase or decrease in the number of neurons, does not mean that these cells are complete unaffected by exposure to methyl mercury. Subcellular and physiological changes are known to occur following mercury exposure," and so the cells in this study were counted by counting their nuclei. Hence, cells, which were damaged, but not killed outright, would still be included by the technique employed in this study."

Do you agree with that as a general proposal that neurons can be dysfunctional without having been killed?

A I agree that they did not detect any neuronal injury in this study. It is possible that had they looked by other techniques they might have found some, and that's what they're saying here. They didn't totally rule out, and certainly if they go to higher doses, they probably would have even seen something, but --

Q Now, earlier I asked you --

A If I could just finish my answer?

Q Sorry.

A Essentially what they're saying here is look, we didn't see any neurotoxicity. It doesn't

mean we can't rule out that any may have occurred that we couldn't see. I would agree with that.

Q Earlier I asked you whether the fact that they detected inorganic mercury in neurons in this study, whether inorganic mercury neurons at the level detectable here, namely in what? At least 10 parts per billion. Would you agree --

A I don't know what their limits of detection were.

Q I asked you if that was a good or bad thing, and I think you didn't answer the question, so let me ask it again. If you've got 10 parts per billion of inorganic mercury in your neurons, is that a good thing or a bad thing?

A Well, from the data we looked at before, we saw that you could have in your brain, which is primarily neurons, you can have in your brain hundreds well in excess of 100 parts per billion of mercury without any clinical effects. That study didn't specifically look at which particular cells they were in, but we know in this study, in the data that was presented here with the neurons accumulating some amounts of mercury that there were no observed adverse effects.

Q When you refer to the 100 parts per billion

studies, you're talking about the studies that looked at total mercury, not inorganic mercury persisting in the brain over time.

A Well, that's right, but that's what most of the mercury that persists in the brain is going to be, is inorganic mercury.

Q Now, the infant monkey study if you'll recall referred after they started talking about the inorganic mercury and what had happened in these adult monkey studies, they refer to this Vargas paper, do you recall that?

A Yes.

Q I want to just hit a couple quick high points in that Vargas paper relevant to what we've been talking about. We can pull it up. This is Petitioners' master reference Exhibit No. 69.

A I don't have a copy of the Vargas paper here.

Q Sorry.

MR. MATANOSKI: Your Honor, just for the record, I don't believe the Vargas paper has been discussed by this witness at all.

SPECIAL MASTER VOWELL: All right. And you're objecting based on --

MR. MATANOSKI: I'm not sure. I guess I

would like to see if the next question is going to go to mercury and a toxicological question as opposed to a neurological question.

SPECIAL MASTER VOWELL: Let's hear the question, and then we'll decide. Go ahead, Mr. Williams.

MR. WILLIAMS: I do believe he discussed the Vargas paper on direct, and it's cited in the monkey study as a relevant study, and part of what I'm trying to establish is that he didn't examine all of the relevant literature as he claims, but nevertheless, let me see if I can make this relevant even to you.

BY MR. WILLIAMS:

Q Let me ask it this way. Do you agree that it's part of a neurotoxicologist's job to determine whether or not an agent could provoke neuroinflammation?

A Sure.

Q Okay. Let's look at the abstract, just the last half of the abstract if you can blow that up and highlight it a little bit? It says, "We demonstrate an active neuroinflammatory process in the cerebral cortex white matter and notably in cerebellum of autistic patients," and then they talk about some of the biomarkers they found.

They say, "Our findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients suggesting that future therapies might involve modifying neuroglial responses in the brain."

MR. MATANOSKI: Now I will object.

SPECIAL MASTER VOWELL: Mr. Williams, I need to understand kind of where you're going here because I don't find Vargas cited in the infant monkey study in Burbacher unless I'm spelling it wrong. I was just trying to put myself wherever the witness was. It's Vahter, but I don't find Vargas.

MR. WILLIAMS: If you look, Special Master, at page 6 of the infant monkey study?

SPECIAL MASTER VOWELL: Okay.

MR. WILLIAMS: This is Exhibit 26, page 6, there's this long discussion of the adult monkey studies in the right-hand column. At the very end of that column or paragraph it says, "It is important to note that an acting neuroinflammatory process has been demonstrated in the brains of autistic patients, including the marked activation of microglia, Vargas, et.al.

SPECIAL MASTER VOWELL: Okay. It's just not coming up when I do a search. All right. Thank you.

MR. MATANOSKI: What I suggest, Your Honor, is that the question be limited to the discussion of Vargas in the Burbacher paper rather than to a discussion of Vargas itself, which in the highlighted part I see nothing that discusses mercury at all in that. The question posed to --

SPECIAL MASTER VOWELL: I understand your objection such as it is, and if Dr. Brent can answer, he can answer, and if he can't, I'm sure he'll tell us that it's outside his area of expertise.

MR. MATANOSKI: Thank you, ma'am.

SPECIAL MASTER VOWELL: Go ahead.

MR. WILLIAMS: With all due respect to Mr. Matanoski, I don't believe he was --

SPECIAL MASTER VOWELL: I ruled.

MR. WILLIAMS: I'm sorry.

SPECIAL MASTER VOWELL: Just move on, Mr. Williams, please?

BY MR. WILLIAMS:

Q I read the sentence that said, "Our findings indicate that innate neuroimmune reactions play a pathogenic role here." One of your slides seemed to criticize Petitioners here for having one theory in the Cedillo case about suppressing the immune system and a theory about stimulating the immune system, but

isn't there a big difference between the adoptive immune system and the innate immune system that is implicated in this paper?

A Well, let me answer it this way. First of all, let me clear up a misconception of something you said. I did not refer to the Vargas paper on my direct testimony. Secondly, I have read the Vargas paper, and I can tell you the word "mercury" exists no where in this paper. Thirdly, whether you're talking about the adoptive or the innate immune system, you're basically talking about some components of the immune system being stimulated.

Q But you do agree that in the Cedillo case, the focus of the thimerosal damage to the immune system was on the adaptive immune system, correct? The ability to kill viruses?

A If you read my cross-examination by Ms. Chin-Caplan in the Cedillo case, you will find that she cited multiple high-dose studies dealing with different aspects of the immune system and immunological responses.

Q If we turn to page 12 of this Vargas paper, in the left hand column at the very bottom, I'm going to agree with you it doesn't mention the word mercury. However, it says that, "One alternative explanation of

this inflammatory process is that extrinsic causative factors, for example, nongenetic neurotoxic or environmental, involved in the pathogenesis of autism may produce neuronal and cortical abnormalities to which neuroglial reactions are only secondary responses," do you see that?

A You read that correctly.

Q And again, is it your opinion in your expertise in neurotoxicology that an agent that could ignite the neuroinflammatory process is described in this autopsy study of autistic people, any neurotoxin, whether it's mercury or a virus that could ignite that process should be on the list of potential etiological factors for autism?

A When you say "on the list of potential," you mean on the list of factors that might cause autism, a list of factors that might be investigated as a potential cause of autism? I'm not sure I understand your question.

Q My question is do you agree with the statement made in several of these papers that an agent that can provoke a neuroinflammatory reaction is a suspect for causing autism?

A I would have to say as a medical toxicologist that is a question that would be best

directed to a neuroscientist.

Q Have you looked at the terbutaline situation? Terbutaline is a toxin, correct?

A Terbutaline is an FDA-approved drug. Like any drug, depending upon dose and so on, it may have adverse effects.

Q My question is when you were doing your thorough and careful review of all the relevant literature, did you look at the terbutaline model of provoking autism and neuroinflammatory responses?

A Not really. I looked briefly at some of the epi. It did not seem relevant to anything I was discussing. I did not include that in my report. It was not something in my discussion. I did look briefly at it. I've heard much discussion of it here. I will tell you in my opinion from only what I looked at briefly, I think the discussion is a bit overblown with regards to the degree of association and whether such an association actually exists, but other than that, I cannot say anything more about terbutaline.

Q Well, you say it's overblown. Let me just quickly make a couple of points here, and then we'll move off this topic, but if we look at the Connors paper, which is Petitioners' Exhibit 73 --

A I don't have that. Thank you.

SPECIAL MASTER VOWELL: And you were referring to Petitioners' Master List? There may be a different number of Petitioners' exhibits.

MR. WILLIAMS: I'm sorry. Petitioners' Master Reference List 73, page 1. I just want to show the title and the authors here.

BY MR. WILLIAMS:

Q Do you see that this is the group from Johns Hopkins including Dr. Andrew Zimmerman as well as Dr. Connors?

A Yes.

Q You're familiar with this group of researchers, aren't you?

A I know Dr. Zimmerman.

Q And just to show you quickly the point of the paper if you blow up that abstract? It says, "Continuous terbutaline exposure for two weeks or longer was associated with an increased concordance for autism spectrum disorders in dizygotic twins and a further increase in the risk for male twins with no affected siblings." Now, don't you agree that's evidence that terbutaline may be causing autism in some children?

A That is evidence of an association in one particular paper. I'm not even sure I see a

statistical analysis of that. Let's see. Here it is. No. That deals with the polymorphism. That by itself would to me certainly raise the question that there might be something there, but as I said before you have to look at the totality of data. You can't simply look at one association study.

As a matter of fact, if you look at the p values I see here in Table 2, it's a nonsignificant p value. It's a nonsignificant association to the total group. If you look down in the bottom on that one particular group, no ASD sibs or male/female sets with a relative risk of 4.4, that's the one positive p value. Based on that, I don't think you can make a global causation conclusion. It's a bit of data.

It's a bit of data that certainly warrants further looking at, but I don't think you can conclude definitively that terbutaline causes this. There are many through association that don't actually involve causal relationships.

Q So if a physician was trying to run through the possible causes of autism in a child, you wouldn't consider putting terbutaline on the list of possible agents?

A If somebody said to me I have an autistic child in my practice, and that child received

terbutaline prenatally, is that likely to have been a contributor? I would say the jury is out. There is some data that it might be, but we don't know for sure yet.

Q Now, in fact this group has done a little bit more research on this. Just briefly again if we pull up Petitioners' Master Reference List No. 106, which is the Zeratte paper, and let me get a copy for the witness.

A Thank you.

Q Now, the title of this paper is Neuroinflammation and Behavioral Abnormalities After Neonatal Terbutaline Treatment in Rats, Implications for Autism, and again the authors here, Zeratte is the first author, but we have Connors, Vargas, Zimmerman and Pardo. That's again a highly-respected group at Johns Hopkins, right?

A Yes.

Q And just to show the abstract in the conclusion -- I don't want to bother with that. Let's go over to the other side. It says, "Our findings indicate that overstimulation of these receptors during an early critical period results in microglial activation associated with innate neuroinflammatory pathways and behavioral abnormalities similar to those

described in autism," correct?

A That's what it says.

Q So these authors, these investigators at Johns Hopkins have not only found an association between terbutaline exposure and autism, in an animal model they've found that it appears to be a neuroinflammatory process.

A They have not said that this data shows that terbutaline causes autism. I haven't seen anybody make that kind of definitive statement. This is an area of active research. I think people are looking at it. There is some data out there that people are looking at, but I haven't seen any definitive statement by anybody. I haven't seen any definitive study on this topic.

All I can say is it's out there. It's one of the many things that's under investigation in medicine. There may be something to it. There may not when everything shakes out.

Q Now I just want to review the papers we've gone through and ask you a question about each one. the first one is the Burbacher/Clarkson infant monkey study published in '05. It was discussed and cited in your report as well as in our reports back in August of '07, and my question is do you agree that that's a

relevant paper for the Special Masters to consider?

A It is.

Q Okay. The next one was the five papers on the adult monkey studies. Those were not cited or discussed in your report, although they were in our reports back in August. Do you agree that those are relevant studies?

A Well, let me point out a couple of things about that. I mentioned on a number of occasions why I found those studies uninformative about the question of whether thimerosal-containing vaccines contribute to autism. Those studies provide no information about that, nothing useful that can be used for that. You may consider that I'm a medical toxicologist. My role here is to comment on the theories put forth and the hypothesis put forth by Dr. Aposhian. Dr. Aposhian didn't discuss this paper.

Q Do you think that this is a relevant paper for the Special Masters to consider?

A I will say again I see no way that this paper can be informative to anybody about the question of whether thimerosal-containing vaccines induce autism. The paper is not even about autism, and if in a matter of fact, if one were to try to take away from these papers that inorganic mercury somehow is related

to autism, then you have to look at where our major exposure to inorganic mercury is, and our major exposure to inorganic mercury is methyl mercury through food and through breastfeeding.

Q You have said that several times. My question is do you think this is relevant or not?

A I was just trying to explain to you why I felt this was not a relevant paper.

Q The Vargas paper that talks about neurotoxins as a possible cause of the neuroinflammatory process as seen in autism, is that a relevant paper?

A I will point out to you that whether it is or is not a relevant paper I cannot comment on because it did not deal with mercury. That's what I'm here to discuss. It was not a toxicology paper. In terms of any mercury-related issues? No, I find it irrelevant. In terms of other issues here related to these proceeding? I can't comment. It may or may not be.

Q So you don't know? Is that a fair way to characterize it?

A I'm telling you that has nothing to do with the issue of mercury and thimerosal-containing vaccines. Whether it has to do with other issues that come up in this proceeding, I cannot comment on.

Q Okay. Pardo autism review paper, you probably feel the same way about that?

A It did not mention mercury. It's not a mercury-related paper. I just really don't want to be offering opinions that are far outside of my area. Knowing myself if I did, I would probably say something wrong, that was incorrect.

Q So it would be fair for us to put in here irrelevant from a toxicologist point of view?

A Yes.

Q That would be the right answer?

A For the Vargas paper?

Q The Vargas paper and the Pardo review of the Vargas paper.

A From a toxicology point of view, yes. That is outside of my area of expertise.

Q Okay. Right. And then the Courchesne review, which I didn't show you here just to save time, but that's the one that talks about anything that can ignite this neuroinflammatory process?

A The Courchesne review was not about mercury. I specifically said in discussing Dr. Aposhian's six pillars that I was only going to address five of them. One of them was Courchesne, which was not a toxicology paper, and I was not going to address it.

Q I remember you saying that, and then the Connors and the Zeratte studies on terbutaline and this neuroinflammatory property?

A My testimony here dealt with mercury and thimerosal-containing vaccines, not with terbutaline.

Q Let me ask you this. Do you agree that there are some identified post-natal agent exposures that can cause autism?

A That would be best asked of an autism expert.

Q Okay. On page 27 of your report, and we can get it out. You say that thimerosal-containing vaccines do not cause accumulation of mercury in infants.

A Can you show me where that is?

Q Sure. Let's pull that up if we can, and I'll identify it by exhibit number.

(Discussion held off the record.)

THE WITNESS: Can I get a copy of the report?

MR. WILLIAMS: Respondent's Exhibit G, page 27.

THE WITNESS: Page 27? Okay. Please go ahead.

MR. WILLIAMS: I may have written it down

incorrectly. No. It's there.

BY MR. WILLIAMS:

Q In the middle paragraph of page 27, it says, "Therefore, because the ethyl mercury from episodic vaccinations is rapidly eliminated, the exposure is not continuous, nor is it cumulative." Right in the middle of the page.

A Right.

Q Now, based on our review of the Burbacher infant monkey study and the adult monkey studies, do you agree now that that's an incorrect statement?

A Not really. I mean, you could talk about the fact that whenever you get a vaccination, most of the mercury is eliminated. You get a small amount that remains in the brain, but it is so minuscule compared to the brain concentrations of mercury that you really don't get any significant bioaccumulation from it.

Q Just a couple of more points. You mentioned the Easter case?

A Yes.

Q The child was unsuccessful in federal Court?

A That's correct.

Q You actually testified at the hearing in that case, didn't you?

A No.
Q Just by deposition?
A That's correct.
Q You do know that Judge Ward specifically said he was not ruling on general causation. It was only a specific causation question, do you agree with that?
A I don't remember that particular language.
Q And that he also told the child and the child's parents that when they have stronger evidence they could come back. He didn't dismiss the case forever?
A I don't recall that, but I'll accept your interpretation.
Q Then the final question is this: We know that the Burbacher group is looking at the pathology of those infant monkey brains to see if they find the same neuroinflammatory processes in the adult monkeys or what else they find. Do you think it's appropriate for your or for the scientific community in general to close the door on the question of whether thimerosal can cause autism before we know the results of that study?
A I would have to say this: There's always people doing more studies on more things. If somebody

has funding to do a study, they're going to do the study. At this point, my position is very much the same as the IOM and all the rest of these organizations that resources would be better spent other places that there is an overwhelming body of evidence that thimerosal-containing vaccines are not associated with autism. People will continue to do studies from time to time.

I don't think you can say that one should not take a position on what the huge body of medical literature says based on waiting for one particular study to be published.

Q I don't want to let you escape with the word autism versus regressive autism, so let me put the question to you again.

A Sure, sure.

Q If the Special Masters are considering the question of whether thimerosal leading to inorganic mercury in the brain leading to neuroinflammation can cause autistic symptoms. Do you think that they would be good to wait for the results of that brain study or not?

A You have to look at it like this. That's kind of illogical because Burbacher's monkeys were presumably normal monkeys. We've heard testimony here

that there was this subset of susceptible individuals who get regressive autism from mercury, and everybody else just does find with their vaccines. There is no logical reason to possibly conclude that the Burbacher monkeys represent a susceptible subpopulation that's likely to get regressive autism, so that wouldn't even be the right model to look at that.

Q What about the terbutaline study on rats that look at neuroinflammation. Are you saying that's a useless study then, too?

A I didn't say it's useless. I'm just saying it's uninformative about the question about whether thimerosal from vaccines causes autism.

Q Regressive autism.

A Any kind of autism.

MR. WILLIAMS: Thank you.

SPECIAL MASTER VOWELL: Respondent, any further questions for Dr. Brent?

MS. RENZI: I just have a few followup questions.

REDIRECT EXAMINATION

BY MS. RENZI:

Q Dr. Brent, I just want to clarify some questions Mr. Williams asked you about the series of Vahter papers.

A Yes.

Q He talked about the doses of the inorganic mercury that was administered to the monkeys in that study?

A He did.

Q Could you discuss those doses and how they relate to the question at hand?

A Sure. That was the point that I had tried to make that if you look at that study that shows inorganic mercury deposition in the brain and microglial activation for whatever reason that is due to the inorganic mercury. The inorganic mercury in our brain comes primarily from methyl mercury from seafood, from breastfeeding, from even chicken.

If that study actually represented a model of autism, then we would have an awful lot of autism from breastfeeding, and we would have an awful lot of autism from seafood, so it can't possibly represent an appropriate model.

Q And what was the significant, if any, to the findings that were in the calcarine sulcus cortex?

A Right. Yes. That was one of the areas in the brain that was looked at by the Charleston and Vahter studies, and that is a particular area of the brain that is a target area for mercury, so certainly

when you give those kinds of doses of mercury, you're going to see effects in that particular area. It involves the visual pathways.

Q And did those papers actually discuss astrocyte death?

A No, no, no. It did not actually show astrocyte death.

Q And I know you've discussed and said several times that those monkeys shows no clinical symptoms, is that correct?

A That's correct.

Q So accepting the results of the Vahter study, what does this tell you about clinical findings you would expect to see with thimerosal-containing vaccines?

A Well, I'm sure the Vahter study data is valid. I'm sure it's a good study. It comes from a good lab, and I accept the results as they're published. What it tells us is that if you give these very high doses, you get this neuroinflammation. Excuse me. They didn't show neuroinflammation. You get this microglial activation. We don't know what it means or what the significance of it is because the monkeys were clinically fine.

All of us have microglial activation under

some circumstances all the time, but if that process once again were to lead to autism, and inorganic mercury was the cause of autism, then it would be our major sources of inorganic mercury, which are breastfeeding and food and diet.

Q And what do these series of studies with adult Macaques tell you about thimerosal-containing vaccines causing autism in infants?

A Well, those studies didn't deal with autism to begin with, so the studies themselves really don't deal with autism, and therefore there's really no conclusion you can reach about that.

Q And another clarification, and I'm going to go back to the Burbacher paper, the doses of the 20 micrograms per kilogram administered to the monkeys over four different vaccines?

A Yes.

Q What would a child have to weigh to receive 80 micrograms per kilogram of ethyl mercury over those first six months of life?

A We did a little back of the envelope type of calculation at lunch. It turns out to get that amount from vaccine, a child would have to weigh 2.3 kilograms at six months, a rather unlikely scenario.

SPECIAL MASTER VOWELL: 2.3 kilograms?

THE WITNESS: Four and a half pounds.

SPECIAL MASTER VOWELL: Could you convert it to those of who are --

THE WITNESS: Four and a half pounds.

SPECIAL MASTER VOWELL: Four and a half pounds at six months?

BY MS. RENZI:

Q If the mode of injury discussed today is inorganic mercury, why isn't this happening to people without thimerosal-containing vaccines?

A That's the exact question I've been raising all day. Children today and all throughout time have been getting methyl mercury converted to inorganic mercury at doses in excess of what they get from vaccines just from breastfeeding not to speak of diet.

Q And if we assume that microglia continue to stay active solely because of the presence of inorganic mercury, what can we assume will happen because of this exposure to inorganic mercury from dietary sources in humans?

A Well, this was demonstrated of course throughout a high-dose experiment, and if indeed it's very, very low doses of inorganic mercury from either breastfeeding or from vaccines were to cause microglial activation, then as individuals continue to

take in methyl mercury through their diet, their microglial activation would just continue to increase and increase and increase, and we would all have very high degrees of microglial activation.

Q And the last question. Is there anything else you'd like to comment on today?

A I think I've commented quite a bit. You're all probably quite tired of hearing from me.

MS. RENZI: I have no further questions.

SPECIAL MASTER VOWELL: Mr. Williams?

MR. WILLIAMS: Nothing.

SPECIAL MASTER VOWELL: I have a couple of questions for you. You can't quite leave, Dr. Brent.

THE WITNESS: Please. I want to take you back to the Burbacher article briefly.

THE WITNESS: Yes. Sure.

SPECIAL MASTER VOWELL: As I'm reading the article and hearing the testimony, the researchers there used equivalent doses of methyl and ethyl mercury.

THE WITNESS: That is correct.

SPECIAL MASTER VOWELL: One administered intramuscularly and the ethyl mercury and the other administered orally of methyl mercury.

THE WITNESS: That is correct.

SPECIAL MASTER VOWELL: And let me phrase this in terms first of lethal dose. If we're talking lethal dose of ethyl mercury versus lethal dose of methyl mercury, are we talking the same amount, or is there some rough equivalency that one measure of ethyl mercury is equivalent to one of methyl mercury.

THE WITNESS: The study that I can think of that address that was the 1985 study of Dr. Magos where they gave equivalent doses of methyl and ethyl mercury, and they found that for the same does, you actually get a bit more neurotoxicity from methyl mercury than from ethyl mercury anatomically.

SPECIAL MASTER VOWELL: But you don't have any idea of what the equivalency is?

THE WITNESS: It wasn't a huge difference because they then gave I think about 20 or 30 percent higher of ethyl mercury than methyl mercury, and they found a similar amount of damage as they did in the lower dose of methyl mercury, so methyl mercury is about 20 or 30 percent more neurotoxic than ethyl mercury in that study.

SPECIAL MASTER VOWELL: In terms of how much mercury ends up in the brain as inorganic mercury, can you tell me the difference between the necessary dose of methyl mercury versus a dose of ethyl mercury? Is

there any comparison? I apologize for being inarticulate, but it sounded as if --

THE WITNESS: No, no, no. I absolutely understand your question. If you look at the Burbacher study, then you see that the amount of mercury in the brain following thimerosal administration ends up being primarily inorganic mercury, and I think we looked at a number. It was over 10. I think I saw a number of 16 or something of that, parts per billion. If you look at what happens when you give the equivalent dose of methyl mercury, and I wonder if we could bring up the Burbacher methyl mercury slide?

In fact, why don't we put them next to each other so you can exactly the mercury concentrations that are achieved under both circumstances. Okay. So on the right, you have thimerosal, and as you can see, the data finds the amount of inorganic mercury, and it's something of a lower 10, and the ethyl mercury at its peak looks like 10, 20, something between 20 and 30 parts per billion. It rapidly goes away.

Methyl mercury at a similar dose gives the levels that you see here, maybe about seven parts per billion of inorganic mercury, but on top of that, the organic mercury is up at about 100 parts per billion,

so it is far, far in excess a similar dose of methyl mercury. It gives you far, far more combined organic and inorganic mercury in the brain than you will get from ethyl mercury, and this is the best comparison I know.

SPECIAL MASTER VOWELL: And your testimony then is that organic methyl mercury will be converted to inorganic mercury but albeit at a slower rate than the ethyl mercury on the right slide that's already been converted to?

THE WITNESS: Well, to be scientifically precise, we know that methyl mercury is slowly converted to inorganic mercury. It is possible that not 100 percent of it will do that. Some of it may actually leave the brain. We don't know. What we do know is that the difference in the mercury concentrations at the beginning of the experiment all the way on the left, if you look at Figure 4, and at the end of the experiment on day 28 on the right are not significantly different from each other.

That would suggest that if any leaves the brain at all, it's a very small and nondetectible amount. That which remains behind, yes, will be ultimately converted to inorganic mercury.

SPECIAL MASTER VOWELL: I think those are my

questions. Questions from the either side based on my question? Do either of my colleagues have any questions? Apparently not. Other questions?

MS. RENZI: I have one more for Dr. Brent.

SPECIAL MASTER VOWELL: Go ahead.

REDIRECT EXAMINATION (RESUMED)

BY MS. RENZI:

Q Dr. Brent, if Dr. Burbacher were to publish in the future findings of microglial activation in the infant monkeys that he studies, similar to the findings described in the Charleston and Vahter papers, would that change your opinion here today?

A No. They couldn't. I'm just testifying about inorganic mercury from any source because it's the same inorganic mercury, and so if there is microglial activation, that microglial activation can just as well come from and more likely would come from the much larger doses of methyl mercury from breastfeeding and diet.

MS. RENZI: I have no further questions.

SPECIAL MASTER VOWELL: Mr. Williams?

MR. WILLIAMS: Nothing.

SPECIAL MASTER VOWELL: Dr. Brent, you're excused.

THE WITNESS: Thank you very much. I

appreciate your patience.

(Witness excused.)

SPECIAL MASTER VOWELL: It's 3:15. Do you want to see to your next witness or take a mid-afternoon break? What's your preference? I know it would be early to take a mid-afternoon break. I'm just trying to get a feel for where you expect things going today?

MR. MATANOSKI: Could we take a brief break just because we have to switch counsel anyway at this point?

SPECIAL MASTER VOWELL: Ten minutes?

MR. MATANOSKI: I just turned to Ms. Renzi, and I said what would you like to do, and she said I'm done, so she's going to definitely take her break, but we have to do a little switching anyway.

SPECIAL MASTER VOWELL: How much time? Five minutes? Ten minutes? What do you need?

MR. MATANOSKI: Five minutes maybe, or would you rather make this an afternoon break? I believe this witness will be fairly short on direct.

SPECIAL MASTER VOWELL: I'm sorry?

MR. MATANOSKI: I believe this witness will be fairly short on direct.

SPECIAL MASTER VOWELL: Any projection on

how short is short? What we're trying to decide is whether to give you a long break now and then proceed straight through otherwise or --

MR. MATANOSKI: I understand it will be about an hour, perhaps a little less. Would you like to take our afternoon break in light of that?

SPECIAL MASTER VOWELL: Let's just take five minutes now.

(Whereupon, a short recess was taken.)

SPECIAL MASTER VOWELL: All right. We're back on the record, and we have Dr. Mailman on the stand. Would you raise your right hand, please?

Whereupon,

RICHARD B. MAILMAN

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

SPECIAL MASTER VOWELL: Thank you. Ms. Babcock, you may proceed.

MS. BABCOCK: Could you distribute the slide presentation, please? This is Respondent's Trial Exhibit 5.

(The document referred to was marked for identification as Respondent's Trial Exhibit No. 5.)

SPECIAL MASTER VOWELL: And do we have copies for us?

MS. BABCOCK: Yes.

DIRECT EXAMINATION

BY MS. BABCOCK:

Q Good afternoon. Could you please state your name for the record?

A Yes. My name is Richard Bernard Mailman.

Q And could you briefly describe your collegiate and graduate education?

A Yes. I received a bachelors degree in chemistry and food science from Rutgers University. Following that, I earned a masters and PhD in physiology with a minor in toxicology from North Carolina State University. Following my PhD, I did postdoctoral training in both drug metabolism and then neuropharmacology at the University of North Carolina School of Medicine.

Q And what is your current academic position?

A I'm currently a professor of psychiatry, pharmacology, neurology and medicinal chemistry at the University of North Carolina School of Medicine.

Q And what are your professional responsibilities, and how is your time split up between teaching, clinical research, administrative

duties?

A My position is largely a research position. I spend about two-thirds or 75 percent in research related activities, and there remaining time is spent in teaching and training of graduate students, medical students, residents and professional students and other kinds of programs.

Q And could you please tell the Court about your current research focus?

A Certainly. Actually, if you could turn to the second slide, these are actually an illustration of two journal covers, which we were fortunate to have our papers highlighted on, and essentially my interest is in the structure, function and signalling of dopamine receptors and the use of that information to design drugs. If you turn to the next slide, I guess I'm not a public person, but we were very fortunate that one of our papers was identified as a hot new area of pharmacology, and I think this is the first public interview I've ever had conducted online.

SPECIAL MASTER VOWELL: And that's page 3.

THE WITNESS: That's page 3. Thank you.

BY MS. BABCOCK:

Q So it's safe to say you've published on the topic of dopamine receptors?

A Yes. I think I have over 170 peer-reviewed publications and probably about half that many chapters, and I would say probably at least two-thirds of them involve dopamine receptors.

Q And are you on any editorial boards, or do you review for professional journals?

A Yes. I'm currently on three editorial boards, and I've actually probably did another eight or 10 over the years of rotating service, and in addition I review papers for journals, probably about 15 or 20 different journals a year.

Q Now, did you review the materials and literature in this case as it relates to your area of expertise?

A I did.

Q And you also prepared an expert report, which has been filed in this case, I believe Respondent's Exhibit AA. You also listened to the testimony of Dr. Deth?

A I did.

Q Now, out of curiosity, was this the first time you've ever been asked scientifically to consider this or you ever considered this general issue from a scientific standpoint?

A Interestingly, I am married to a research

neurologist, who also has a PhD in pharmacology and toxicology, and we were very fortunate that she became pregnant in 2001, and at that point in time, this issue was receiving a lot of press. I think a paper in nature we remember, so my wife and I as both scientists and having an interest in the issue had to review it as carefully as we could to try and make a decision about what we would do with our unborn child.

In fact, we did do that review, and our child was vaccinated we're happy to say, and so while that review is a little less thorough I think than all the materials submitted here, we certainly took it very seriously, and acted on our view of the literature.

Q Now, I'd like to start with expanding on some of the issues in your expert report starting out with a conversation about scientific method generally on Slide 4 right now. We've heard the terms hypothesis and theory used in this trial. Could you explain these terms to us as it relates to scientific method?

A Yes, I would be glad to, and I must say these are terms that are too often misused that actually have very precise meanings.

Q And let me interrupt for a moment now. I'm

sorry. We switched quickly to Slide 5 just so the Court can follow along later.

A Right. So essentially a hypothesis is an idea that one has about why something occurs or what might be a result of a certain phenomenon. This can come from a bad dream. It can come from a lightbulb going off in your head. It can come from hearing somebody else speak about their work. It can come from somebody else's ideas, and I think this is one of the creative parts of science is how to generate hypothesis.

However, the scientific method demands something that's not generally appreciated, and that is one should seek to disprove one's own ideas, not to prove them, and it turns out there's quite a large difference in these two types of approaches. Essentially, disproving an idea is to test it rigorously and look for ways to show that the idea is wrong.

The notion behind this is that if one does that over and over again, and you fail to disprove a hypothesis, that hypothesis then gathers additional weight and eventually if that's done by multiple investigators and done critically, one then develops what is called a theory, so a theory is actually a

much higher level idea than a hypothesis.

Although the term is sometimes used in a flippant kind of sense, a theory really means an idea that has been investigated relatively rigorously and is generally believed to be true, not something that one speculates about. Ultimately, if a theory is tested again continuously and it's never found to be false, one may actually turn it into a law.

Now some theories are later disproved. Even some laws are later disproved, but these are sort of the echelon of scientific ideas, and I think it's very, very important when one considers any scientific idea, but especially one that has such broad ramifications to remember how we should approach these types of problems.

Q Now, have you been involved in this sort of approach as it relates to controversial hypotheses before?

A In a sense, I was dragged into something about 25 years ago. If you can have it out in the next slide please, and this related to the issue --

Q Slide 6.

A This is Slide 6. I'm sorry. This is related to the issue of whether food colors cause childhood hyperactivity, and if you can add Slide 7,

please? In 1974 I believe, a pediatrician named Benjamin Feingold published the book called *Why Your Child is Hyperactive*, and he essentially said that most, if not all, of childhood hyperactivity is really due to dietary factors.

That is that children who would ingest synthetic food colors, coupled with a couple of natural ingredients that are found in some foods, the synergy between those two would actually cause most of childhood hyperactivity. Now, obviously if something like this were true, it provides a very easy way to eliminate this very important medical problem. He advocated a certain kind of elimination diet in his book and parents in open kinds of ways started following this diet.

We started getting a lot of anecdotal reports of its dramatic effectiveness. People would swear by it. The medical community picked up on this and of course then designed controlled clinical trials to test this, and you can imagine how to test a diet where you take out a lot of things that children would normally eat, plus have to test food colors, which are very easy to see visually. They ended up having to use a black cookie to give to the kids, so whatever.

Those controlled trials suggested that in

fact the diet did not have effects, but while this work was going on, a paper appeared in science, if you turn to Slide 8, by Lafferman & Silbergeld, and essentially what they reported in this very high-profile paper was that one of these food colors in particular, Red No. 3, actually seemed to be the main culprit.

They postulated that there was a mechanism involving my favorite neurotransmitter called dopamine that actually why this food color could cause children to be hyperactive. Now, when this paper was published, we reviewed it very carefully, and what we saw in relationship to what I talked about with the scientific method was that aspects of that work were not well controlled and that there were ways that they should have examined this hypothesis further before actually publishing a paper of such impact.

We felt strongly enough about it that we actually went into the lab and did those very studies, and if you'd turn to Slide 9, you'll see that science also published our work, and we think we explained that in fact the work of Lafferman & Silbergeld was an artifact, that it had nothing to do with a real phenomenon that would change the behavior of children, and we went so far as to actually then test that in

rats.

We gave the rats very, very large doses of this food color, and two things were very noticeable: 1) they didn't become hyperactive, but they did become red, so we thought that that was quite good evidence that we'd given an adequate enough dose and that this issue was settled. A few years later, the National Institutes of Health held a consensus symposium to try to really resolve this overall issue.

If you'll turn to Slide No. 10, I've just pulled out -- I'm sorry. Let me just go back a second. In our paper in *Science*, we really put forth like Dr. Brent talked about, you can sometimes speculate in the discussion of papers, and we actually offered our own philosophy, and I underlined that sentence in red.

We said, "Whatever the outcome of future scientific and clinical experimentation," because certainly people can feel free to review these kinds of issues further, "cautious presentation and interpretation of data will prevent expensive and spurious perturbation of the public and scientific consciousness, so we felt especially in areas that are public health relevant, one really has to follow the scientific method very carefully.

Now, again if you turn to slide 11, the National Institutes of Health consensus panel actually reviewed our evidence among other things related to this issue, and I think they came down on the side that 1) Red No. 3 was not something that caused hyperactivity, and in addition, that these food colors and these elimination diets were not really a cure, if you will, for hyperactivity. I think that view has really held up relatively well over the next two decades.

Q Now I wanted to move to a discussion of Dr. Deth's hypothesis specifically as it relates to the D_4 dopamine receptor. From his slide presentation, I think that Slide 29 was probably the best graphical picture of it, which we've just gone ahead and incorporated into Slide 13 in your presentation.

A Right.

Q From your area of expertise, what areas do you agree with, and what do you disagree with?

A Is this the best monitor?

Q Yes, just be clear when you do it to try and describe what part of the picture you're pointing to so it's clear on the transcript later.

A So at least in the initial work that I reviewed, the primary causative mechanism that seemed

to be postulated was an effect on one of the dopamine receptors called the D_4, and that's illustrated at the bottom left-hand part of this cartoon, and essentially Dr. Deth postulates that not only is this the molecular site of action, but in addition that this receptor plays a major role in attention and awareness to the right of that.

This became the focus of my review of this aspect of the matter.

Q And we'll get into the details momentarily, but is it safe to say you disagree with certain aspects and how he's characterized this?

A That's correct. I have strong disagreements with his point of view.

Q Now, what role does dopamine have in the brain, and how does it relate to attention and awareness?

A Right. So this is now Slide No. 14, and it's my cartoon of a cross-section of a human brain. On the top right-hand section just for your information is the structure of dopamine. It's a very central molecule, and as I may comment on later, let me just point out the left-hand part of this molecule has the ring and two OH groups, and this is called a catechol, which actually is I think very, very

important issue that we may discuss later.

SPECIAL MASTER VOWELL: I'm sorry. I didn't get that word.

THE WITNESS: Yes. Catechol.

SPECIAL MASTER VOWELL: Okay.

THE WITNESS: C-A-T-E-C-H-O-L. Anyway, so dopamine is made by nerve cells, and most of those nerve cells, about 80 percent of the nerve cells use dopamine in the brain. They're located right here in the middle in these two round, darker dots, so these are actual cell bodies of the nerve cells, and they send long processes to various parts of the brain.

This area here in the middle is called the basal ganglia. It's very, very important in terms of motor control, some integration of function, and it's an area affected in Parkinson's disease, which Dr. Deth I think mentioned. This area here and here are parts of the cortex, and they play a role in attention arousal, cognition and emotion, and each of these areas comes from one of these two parts here.

The top part here is actually the one important for motor function. The bottom part here is the one important for cognition, emotion and attention.

BY MS. BABCOCK:

Q So are there different dopamine receptors then?

A Right. So what happens? If you can go back to Slide 14 for one second. Thank you. These areas here as I mentioned in the middle are the nerve cell bodies, and they send these long processes, and dopamine is largely released to communicate with other cells where these little forks are located here and here and here in the left-hand side. These are called the terminals.

When a dopamine nerve cell fires when it's electrically excited, it releases a small amount of this neurotransmitter dopamine. Instead dopamine has to do something, and what it does is it binds to proteins called dopamine receptors, and Dr. Deth showed the Court one those dopamine receptors in a picture that I'll show you later. If you go now to Slide No. 15, it turns out we know a lot about these dopamine receptors.

Initially, many years ago people described it based on their sensitivity to certain classes of drugs and divided these receptors into D_1-like and D_2-like, and when molecular cloning took place, we learned that there are actually five different genes that make these kinds of receptors. Two of these

genes make the D_1 receptor family, the D_1 and D_5 are the gene names. Three of the other genes make three other receptors that are called D_2-like.

These genes are D_2, D_3 and D_4, and Dr. Deth actually has placed special emphasis on this D_4 receptor that's at the very bottom of that schematic that I wrote. I would just point out to the Court's attention, on the left-hand side, this looks like as snake run over by a steamroller, but this is actually a cartoon depiction of the receiptor in a 2-D kind of version, so the D_1-like receptors, the square box in the middle as I'll remind you from Dr. Deth's testimony is what's called the cell membrane.

It's made up of phospholipid, and I've seen stems left and right, and I just had a short part of it. These receptors go through that cell membrane seven different times. Every time they go in and out, they make a loop either on the outside here, the three outside loops or three inside loops, and then they have a beginning tail and an ending tail on the outside and inside of the cells.

What you'll notice is that as I've drawn this cartoon, the D_1 receptors and the D_2 receptors actually differ. The D_1 receptors have this very long tail on the inside. The D_2 have a very short tail on

the inside. The D_1 has a small loop here, and the D_2 has a much larger loop here, and that is going to be very relevant to I think Dr. Deth's hypothesis.

Q Now, Dr. Deth showed us a picture of the D_4 receptor, which would be under the D_2-like pictures that you just described, and I don't recall those loops being there, is that important?

A Right. If you would turn now to Slide No. 18 I believe.

Q Sixteen?

A I'm sorry. Sixteen.

Q It's Slide 9 from Dr. Deth's presentation.

A Okay. This was actually Dr. Deth's Slide 9, and now to take my steam rolled receptor and look at hid 3-D illustration. I'm color blind, so the Court is going to have to sort of follow me with the pointer, but this area here, which I think has reds and greens and turquoise --

Q Aqua and red, yes.

A Okay.

SPECIAL MASTER VOWELL: The far right of the diagram.

THE WITNESS: Right. This is the phospholipid membrane that forms the outer boundary of all cells, so here's phospholipid membrane, and

obviously this would extend all the way around the cell. The blue, if I'm correct --

MS. BABCOCK: Yes.

THE WITNESS: The blue part in the middle is actually the D_4 dopamine receptor, and what Dr. Deth talked about is methionine synthase interacting as he shows in his cartoon directly with the receptor. In fact, as you saw in the previous slide, there's a lot of parts of the receptor that actually would be here, and I don't believe there's any evidence at all for this direct interaction of methionine synthase directly with that part of the receptor.

BY MS. BABCOCK:

Q Now, I think the next slide is just we pulled what Dr. Deth said about this slide from last week's audio recording.

A Right. Again, with the Court's permission, we can just skip down towards the middle here. So what he said is that dopamine makes that available for donating a methyl group, and the methyl group is transferred from the receptor to the phospholipid, and the new one to replace it comes from the enzyme methionine synthase and the methylfolate cofactor that it requires.

It startled us to learn that the methylation

of the membrane around the receptor would change the physical properties of the receptor in this local area, and to my knowledge I know of no evidence at all that the physical properties are changed around this area, that this kind of transfer reaction takes place, so while this might be a hypothesis that one would wish to study in the laboratory, the idea that it should be considered prior to having data about it I think it not correct.

Q Now if we switch to Slide 18, this is further support for why there's so much going on down with the loops then?

A Right. So I've taken my steamrolled D_2 receptor, and I've pointed out these large loops that are so very important in signalling, and we now know that these loops in fact interact with dozens of other proteins to give a richness of signalling that I'll tell you about in a little while, and in fact this is a cartoon I took from the literature, which relates to a similar receptor to the D_2 receptor.

I didn't have a drawing available when I tried to put this together, but essentially here is this receptor now in its real location, a very, very small part of it. Here are some of the proteins that interact with these loops, and of course this now

interacts with what are called scaffolding proteins and a whole variety of other signalling molecules and other receptors.

When one has to consider effects of a single compound on a receptor, one must give consideration to all these types of interactions, and I believe that's one of the things that was not done in this particular case by Dr. Deth.

Q Now, in Slide 29 of Dr. Deth's presentation, which we showed earlier, he identified pathways that he stated purportedly were effected by thimerosal. Does the only thing we'd have to consider in affecting dopamine receptors?

A Right. If you can please turn to Slide 19, this is a cartoon that I colored up and lifted from a work of one of my colleagues, Kim Nepay, and he reviewed dopamine receptor signalling a few years ago in a very, very nice way, and I've actually taken a simplified version of his cartoon, but what you can see here are a whole variety of signalling mechanisms that are very, very important for this receptor and related receptors that nowhere were given consideration in Dr. Deth's hypothesis.

Now, the reason it's important is that sometimes one signalling mechanism can synergize with

another signalling mechanism, and sometimes the two can have opposite affects on each other. If you're going to make predictions, even about how a certain compound affects a single cell, you really have to give consideration to those types of interactions, and that was something that was not at all done in Dr. Deth's development of his hypothesis.

Q Now, what you've just described seems like a fairly complex multivariant process. If you were to design an experiment involving this receptor, how would you go about it? How does this relate to what Dr. Deth did?

A Right. Well, what I did is I think one of the crucial papers at least from the information that I examined was a paper by Waly, et. al.

Q PML 257 for the record.

A I'm sorry.

Q It's discussed already, but just for the transcript.

A If you could advance two slides, please?

Q We're now on 21.

A We're now on Slide No. 21, and essentially there are some general approaches to this type of problem that I feel should always be applied and were not applied in this particular case. I've divided

them up into three distinct realms. The first is how do you pick a model system that will give you information that is most relevant to the larger questions you might be trying to address.

Secondly, once you have the model system, one has to use the appropriate kinds of experimental approaches, if you will, to try and disprove your own hypothesis. We would call them controls or references or whatever, and in many cases that can be molecular manipulations, but in the case of the Waly paper, they can also be drugs, which one uses as controls. I felt that there was not a use of appropriate controls in this particular paper.

Finally, one has to take what's known about a particular system in which one works, in this case the D_4 system, and make sure that known factors are controlled in one's experimental design. Again, this was another general concern I had with the work by Waly, et. al.

Q Now, I wanted to talk about each of these three in a little more detail, starting with the physiological relevance of the model. What is the cell line that was used? Now we're on Slide 22.

A Right. So as I summarized in Slide No. 22, Waly et. al. used a cell line called SH-SY5Y. This as

Dr. Deth told you is a neuroblastoma line that is derived from neurons in the periphery that have become immortal, become tumors, and in particular, it's a peripheral tumor line.

There's nothing intrinsically wrong about using this particular cell line in experiments, but one has to really understand that it is going to be limited by the fact that it's derived from a certain type of cell from a certain location that will clearly not reflect every other cell in the body and certainly will not reflect normal neurons.

In my opinion, one of the things that should have been done in this paper at the very bare minimum is to compare this cell line to some other commonly used cell lines and subsequent to actually making this slide, Dr. Deth's laboratory has used some of these other cell lines, and I'm unclear why he didn't come and do parallel studies in some of these other cell lines.

Ideally, by current standards of the last 10 years, what one would do if one found consistent support for a hypothesis in tumor-derived lines, one would then turn to cultured brain neurons that then test that hypothesis, and it's commonly done and certainly was not done in this case, and I think these

latter two factors really markedly weaken what lessons you can draw from this particular study.

Q Now, did you also observe issues with the experimental controls he used?

A I did.

Q Slide 23?

A Right. So if we turn to Slide 23, I just pulled out a couple of points that were very important, and again I'm sort of surprised because Dr. Deth has experience in pharmacology, and I'm unclear why this design was used. When I talked about the receptors earlier, pharmacologists generally talk about drugs that bind the receptors having two opposite kinds of effects, one type of action is this term agonist, which means something that binds the receptor and turns it on.

The other term here in the next blue line is antagonist, and this is a compound that would bind to a receptor and block it. It wouldn't turn it on. It would prevent other things from turning it on, and these are very, very important kinds of drugs that we use as controls in pharmacological experiments. In the paper by Waly et. al., the only agonist that they used was dopamine, which is the endogenous neurotransmitter and certainly an important one to

use.

The problem with dopamine as I've summarized here is that it will at various concentrations bind to other receptors, other dopamine receptors if they're present and also receptors of similar chemical families or neurotransmitter serotonin or norepinephrine, and it turns out that this cell line that he used actually expresses other dopamine receptors as well as serotonin antinergic receptors.

It should have been obvious to control for those factors, and the use of dopamine alone didn't do that because it could have affects through many of these receptors. Then they used an antagonist as an important experimental control. Again, the same rules apply. You want to use the most selective type of antagonist, which will bind to only one receptor. They used a compound which is known to bind to more than a dozen different receptors as opposed to selective antagonist.

Again, I've since found out that in some of their earlier work, they actually knew about these selected antagonists, so it's absolutely unclear why they were not used in this study, but not doing that I think markedly weakens the conclusions that one can draw.

Q Now, was their also a failure to integrate the data into what's known about D_4 receptors, Slide 24?

A That's correct, and essentially what Waly et. al. attempted to prove was that the D_4 receptor was responsible for this phospholipid methylation they felt was so important. One of the things they did is use a technique called gel electrophoresis to try and isolate this band, but nowhere did they tell us which of the D_4 receptors was present.

As you probably I believe heard, there are several different forms due to a 48-base pair sequence that can be repeated in this receptor, and these are called $D_{4.2}$, $_{4.4}$ and $_{4.7}$ as you can see in the bottom line of this slide. These all have different molecular weights, and the paper never attempted to say which one of these molecular weights they were actually measuring, and for a variety of reasons I think it makes the identity of the particular protein that they sort of called the D_1 receptor less clear.

Another factor of course is that the antibodies that they used combined to other related proteins, so again, this was another factor that made me question whether or not their conclusions were really valid.

Q So is it safe to say if you had reviewed this paper for publication, would you have recommended acceptance?

A I don't think so. I think certainly while the hypothesis may have been worthy of testing, the paper probably I think would have been sent back by most editors or good reviewers with the suggestion that they needed to do more experiments of the type that I mentioned here.

Q Now, are you aware that Dr. Deth both in his testimony last week and also in his expert report has discussed some unpublished data?

A As I was listening to his testimony, I did in fact hear a discussion of some unpublished data, and as you can see in Slide 25, it reminded me of a quote that my major professor made once in a lab meeting. He's actually a very distinguished English gentleman who normally speaks like he just came from Oxford, but I think his words were it ain't science until it's published.

What he was really telling us is that when you submit a paper for publication, it gives other scientists a chance to review the experimental design, the nature of the hypothesis, ones testing, the methods that one's using and the results and to form

their own conclusion whether or not that agrees with you. Certainly, I think that this is common wisdom that one cannot accept things until they've had full scrutiny from the field.

I guess I was sort of surprised and disappointed that we would hear about such unpublished data, and I was struck particularly by Dr. Deth talking about the changes to the message expression in some brain samples I guess from autistic and control children. Apparently, as I recall his testimony, they used PCRs. Does the Court know what PCR is?

SPECIAL MASTER VOWELL: Painfully, yes.

THE WITNESS: Okay. Then you're probably aware that there are good and bad ways to do PCR for different types of experiments, and I was sort of surprised that we did not hear more of those key details because certainly one could not rely upon that evidence without knowing that.

BY MS. BABCOCK:

Q Now I also wanted to talk about how one takes in vitro studies from the laboratory and tries to determine physiological or clinical relevance. You've offered specific criticisms on the Waly paper and the unpublished data. Assuming proper controls have been used, and we could review the underlying

information and methodology, are there any issues with drawing conclusions from such data?

A If you would advance to Slide No. 27, you've seen this one before, but again the important thing for pharmacologists and cell biologists is to understand that single parts of a sibling pathway don't function in isolation. Dr. Deth talked a great deal about how this event of a dopamine receptor and supposed transfer of methyl groups went into this one carbon cascade.

In fact, if thimerosal was having an effect in the cell on the D_4 receptor, it should also be affecting many other kinds of things, including some of the pathways that I've shown on Cartoon 27. Worse, if you would turn to Cartoon 28, if you'll look at the bottom of this cartoon, the D_2-like receptors, and this could be the D_4 here, also interact in a variety of sibling pathways with other major receptors in the brain.

Q You're pointing to the bottom right-hand corner?

A I'm pointing to the bottom right here. GABA receptors, GABA is a major inhibitory neurotransmitter in brain. Unlike dopamine, it's found everywhere, and dopamine systems can affect GABA function. In

addition, these two things NMDA and AMPA are another class of receptors for the major excitatory neurotransmitter found all over the brain for the excitatory neurotransmitter glutamate, and there's known interactions of these receptors with those receptors.

These are the kinds of things that one has to address even to understand what happens in a single cell before one could possibly then believe you could extrapolate to even a laboratory animal let alone a clinical situation, and this is why I felt that the dangers of doing this are really very high, and I was disappointed that Dr. Deth had made the kind of speculation he did without much, much more exhaustive exploration of these questions.

Q Now, Dr. Mailman, I know you've been involved in dopamine receptor drug discovery as it relates to Parkinson's disease. Is there a particular example you can think of that sort of highlights the difficulties of going from in vitro to in vivo?

A Right. As I was preparing my expert report, I guess the term I also remember hearing in graduate school was deja vu all over again, and essentially I have been involved over the years in another area, as you mentioned Parkinson's disease, where there's been

a major hypothesis related to oxidative stress or oxidative damage and its role in the neurodegeneration of Parkinson's disease. If you could advance to Slide No. 30?

I don't want to go into great detail about this, but the prevailing view in the Parkinson's research community through the mid part of this decade was that levodopa or Sinemet was the most effective drug for treating Parkinson's disease symptomatically first used 40 years ago and still the standard of care in Parkinson's disease because of its dramatic symptomatic effects.

The prevailing view was that despite its dramatic symptomatic events, it was actually a toxic drug and accelerated the course of Parkinson's disease, and it did so because of the same types of mechanisms if you have oxidative stress or damage that Dr. Deth was flirting with.

Q So this was based on in vitro work that had been done in an attempt to apply it?

A That's right, and earlier I pointed out to you the structure of dopamine, and I mentioned that one part of it called the catechol. That catechol part of the molecule oxidizes very readily. Every freshman chemistry student who handles dopamine can

see that, and people believed that was happening in cells and causing damage, and levodopa contains this type of catechol group.

I would say there were probably more than 100 papers that may have demonstrated that this could occur in vitro. In fact, there was another drug that's approved clinically for symptomatic relief that seemed to somehow stop that oxidation, so the prevailing view was that levodopa would make Parkinson's patients worse over time by making the disease go faster, and this other drug would make them better.

Finally, a landmark clinical study was started in the early part of this decade to test that idea, and it was published in 2005. It's the ELLDOPA study. It's a surprise to almost everybody in the field. It was found that levodopa not only was great symptomatic treatment, but it actually made the disease progress less rapidly. It actually slowed the progression of the disease, and I think this is a lesson about how one cannot take even well-designed in vitro studies and just jump into the clinic.

It is a long, painful series of experiments one has to do to be able to be reasonably confident of one's conclusions. In the current situation, we have

only the work from Dr. Deth's laboratory, not well controlled, without replication of other laboratories, and again this same jump to a disease that's even more complicated than Parkinson's where we know what the primary lesion may be.

I think this is for me a really good object lesson on how much weight one can give to this hypothesis.

Q So overall, based on your research, your clinical expertise and your review of all the materials and literature, how much validity do you give to Dr. Deth's hypothesis about thimerosal affecting the D_4 dopamine receptor?

A Well, I wouldn't use validity. I believe there is very, very little support for that hypothesis, and I believe that the odds of it being correct are literally almost infinitesimal.

Q And you hold that opinion to a reasonable degree of scientific certainty?

A I do.

MS. BABCOCK: I have no further questions.

SPECIAL MASTER VOWELL: Petitioner?

MR. POWERS: I'm getting Mr. Williams' abundant materials out of the way here.

//

CROSS-EXAMINATION

BY MR. POWERS:

Q Good afternoon, Doctor. My name is Tom Powers representing the King and Mead families as well as the Petitioner steering committee in these proceedings. In looking over your expert report, there are a couple of times where you describe a review of all the relevant available evidence or all the relevant scientific literature. You mention that a couple of times in your report, correct?

A Can I --

Q Yes, let's go to page 4 of your expert report, and if you look under subcategory IV, there's a sentence that begins, "As an expert in neurotoxicology..." We can get that sentence highlighted.

A Okay. That would be great.

Q Yes. Right there.

A Great. Can you redirect your question, please?

Q Yes. Well, it's just that in your report you do say that you find the available evidence, and you're describing the available evidence. These will not be tricky questions. I just want to make sure I get the scope of your report here, so you're talking

about available evidence you've evaluated and again on page 8 of your report, the last full sentence of your report, which is VI, Summary, it says, "Based on my review of the available scientific literature and Dr. Deth's report..."

A Yes.

Q Okay. So I just wanted to explore exactly what you reviewed in preparing your report, developing your opinion and testifying today. I looked at the reference list that was provided with your report, and I see eight citations to the scientific literature?

A Yes.

Q Sound familiar?

A Yes.

Q Out of those eight citations, five of them appear to be articles or chapters in fact that you wrote back in the late '70s, early '80s and deal with these food additive issues, correct?

A That's correct.

Q There's also an article by Dr. Silverman about a disease not related to autism, correct?

A That's correct.

Q In any of those articles, is metal toxicity discussed?

A Well, if I just clarify? What I was listing

there were things specifically cited in the report. The expertise that I used involves the literature that I read today and have read for the past 30 years, so if I had actually listed all the things that led into the formation of my opinions, you would probably have a document certainly as large as one of those binders, so I did not consider only this information. These were specific citations in my expert report.

My opinions were largely formulated by my expertise in the field, which are defined by hundreds of publications I have and the thousands of publications I've read.

Q And so then talking about the publications that you've authored, in reviewing your CV I will be the first to confess that even the articles for a lay person are uninformative as to what the article could be about, but I was looking for any mention of metal toxicity or mercury toxicity. I found I think five articles that describe lead and lithium, and I'm wondering if beyond lead and lithium you have published any original research involving other metals?

A I have.

Q Okay. What metals would those be?

A They were tin-containing compounds and

organic lead compounds.

Q Any dealing with mercury in any form?

A I have no publications with mercury.

Q Do you have any publications dealing with speciation of mercury?

A I do not.

Q Any publications dealing with the pharmacokinetics of mercury in the brain?

A Absolutely none.

Q Any publications dealing with the toxicity of mercury in the brain?

A I do not.

Q Any original research dealing with vaccines and the reactions that might be engendered in a human brain?

A No.

Q Have any of your published articles dealt with neuroinflammation specifically as a mechanism of any neurological injury?

A Nothing with neuroinflammation.

Q I'm sorry?

A No.

Q Okay. You do cite to your food additives and developmental disorders article. This is Respondent's Exhibit No. 322, and I would like to look

at page -- there's no exhibit page on it, but the text of the original document appears to be page 303.

A I'd like a copy, please.

Q Yes. We'll get one over to you, Doctor, from the stack here. All right. I'll tell you what we can do is we'll go ahead and highlight it on the screen, and I'd be happy to hand you the paper copy. It's a very brief excerpt, and I can see the screen well enough from here to ask you some questions, so we're going to need page 303. Doctor, you have it conveniently highlighted in advance there on your paper, but we're going to highlight it on the screen.

It's the sentence that begins, "It's a cardinal principle in pharmacology..." Essentially, the first half of that paragraph up through the date 1977 that's cited in an article, do you see that?

A Yes, I see that. I do.

Q And it describes, and this is you I guess describing it's a cardinal principle in pharmacology and toxicology that the assignment of an effect to a given compound, if you're an investigator it means that you have to know how the agent that you're studying is absorbed, distributed, and ultimately either stored or eliminated from the body, correct?

A That's what we've written, yes.

Q And that as you describe it is a cardinal tenet of pharmacology and pharmacokinetics too?

A That's correct.

Q Now, in Dr. Deth's report, he actually does that, correct, when he is describing the pharmacokinetics of -- let me finish. You may be anticipating my question.

A I haven't said a word.

Q He describes a process through which thimerosal-containing vaccines break down in the body and are distributed in the body, do you recall that discussion?

A Yes.

Q And do you recall that he described how thimerosal-containing vaccines are quickly broken down into ethyl mercury, correct?

A Yes.

Q And that the ethyl mercury enters the brain, it crosses the blood-brain barrier, correct?

A Yes.

Q It's broken down into inorganic mercury inside the brain on the other side of the barrier?

A Correct.

Q And the inorganic mercury, at least parts of that, are stored in the brain and they accumulate in

the brain, correct?

A Yes.

Q So at least in terms of his methodology of pharmacokinetics, Dr. Deth has satisfied the cardinal rule of pharmacokinetics by describing how the agent that's of interest, inorganic mercury, actually gets into the organ of interest, the developing brain, correct?

A No, that's not correct because what I was really commenting on was Dr. Deth's research that's published, and in fact if you will recall the Waly paper.

Although Dr. Deth had talked about thimerosal being converted to ethyl mercury rapidly, and mercury being the active species, in his experiments he used thimerosal, which clearly means that one doesn't know what's happening because he's now not putting it in an organism, but putting it in a cell type, so while he may be aware of these facts, he certainly did not apply them in the published research that I've reviewed.

That is what I regarded as a cardinal defect, if you will, following my cardinal principle. It's how he took what is basic understandings and used them in his own experiments, and that's the reason I

felt that the Waly paper could not be relied upon as this key piece of information that was the underpinnings of his hypothesis, so whereas he may have talked about it correctly, he did not apply those in his experiments.

Q Now, in his experiment, and we can pull that up, he used this neuroblastoma cell line, correct?

A That's right.

Q And if one is using a neuronal petri culture, is it correct that neurons don't divide, they don't replicate?

A Well, it depends, but that's not generally true. It depends on the state of the neuron. We wouldn't have brains if neurons couldn't divide.

Q But in the in vitro setting, the reason researchers typically use clonal cells lines like this is that they replicate, correct? They replicate pretty predictably?

A We use clonal cell lines because they're immortal, so from time to time we can pull something out of the freezer without having to do the work that's involved with culturing brain neurons, which is much more difficult and which generally you're not able to keep living indefinitely. That's the primary reason.

Q And by immortal part of that is the division process. These are cell lines that as part of that immortality have a predictable replication rate and can grow and divide and are useful in that setting?

A Yes.

Q Okay. Now, in talking about the cell line again, you indicate that there were no testing done basically to control for the dopamine selectivity or the receptor selectivity in that cell line, is that correct?

A That's correct.

Q Now, in making that analysis, did you review Dr. Deth's earlier publications, the 1999 Sharma paper that he cited and the 2001 paper that he was also involved in?

A I had read those papers earlier.

Q And in those papers, doesn't he talk about how he looked for the receptor specificity of this type of cell line and that he had controlled for that in earlier studies?

A Well, that was what was quite surprising because in those studies they were in different cells lines, so 1) the receptor population in this cell lines is actually better known than in this particularly cell lines, and indeed in those studies,

although they weren't perfect, they were better controlled, and that's what made the Waly paper, and it's the one that's really relevant to this case quite surprising because he had a cell line that's not as well understood.

He did not use the type of controls he used earlier, so while those other papers certainly were better controlled, the Waly paper, which is the only one I know of relative to thimerosal was clearly poorly controlled, even by Dr. Deth's own standards.

Q Now, you're saying this cell line is not very well understood?

A Relative to the other cell lines that Dr. Deth used, which are much more widely used.

Q If one were to search on PubMed, for example, and were looking to find papers that use this particular cell line, do you have an idea of how many papers might appear?

A Probably several hundred, maybe 1,000, but if you look, for example, I think it was the CHO cell lines that he used in an earlier paper, you would probably find 100,000.

Q Well, would it surprise you if it was between 2,400 and 2,500 that you can find in PubMed that identify the use of this particular cell line?

A It wouldn't surprise me. As I said, it could be in the area of 1,000. It's certainly though not nearly as widely used as the other common lines in the field that Dr. Deth used earlier.

Q Now, the discussion in Dr. Deth's paper --

A If I could just add one thing? In fact, it's that information that let me know that there are other receptors in that cell line that Dr. Deth should have considered, so in fact knowing that there are other papers there that was I aware of that let me know that he had not controlled things that he should have known to control.

Q But it is your understanding that he did use a very highly selective D_4 receptor ligand, and there's a particular ligand that was used, and he had discussed that at some of the earlier papers leading to the Waly paper?

A That's right. He uses selective D_4 compound in the earlier paper. He did not use that in this paper. The Waly paper is of concern because there are other receptors that dopamine could have interacted with that were not controlled by the ligand that he used. It's my criticisms of the Waly paper, and in fact I think what made it surprising is that Dr. Deth seems to have forgotten things that he apparently knew

a few years earlier.

Q Now, when you talk about the other receptors that are involved, D_4 is involved, but you're saying there would be ones in addition to D_4?

A I didn't. D_4 receptors may be in the cell type, but there are other cell types, which could have interacted with dopamine, which are known to interact with dopamine that were not controlled, so the issue is I can't nor anybody else can make a definitive conclusion about even the limited hypothesis that he was testing because of the experimental design above and beyond the limits that the system itself cannot be used to jump to autism.

You can't even be sure that you have a definitive answer to the narrow hypothesis based on the way that experiment was done, and I will clearly differentiate the quality of the Waly paper from some of Dr. Deth's earlier studies, which were better controlled, so I can differentiate those in terms of quality quite readily, but the Waly paper is the weakest, and it's the only one of relevance here.

Q Now, the other potential dopamine receptors that might be implicated here in addition to the D_4 in the Waly paper, the D_4 is the only one of those that contain methionine synthase, isn't that correct?

A No, that's not correct. The D_4 does not contain methionine synthase.

Q Does it contain a remnant of methionine synthase?

A It does not contain a remnant of methionine synthase to my understanding.

Q To your understanding?

A And to the literature understanding, at least as far as I know.

Q But if it had a remnant of methionine synthase, that would at least support the idea that that's where the methyl group is becoming available at that point, correct?

A I would have to see data to that effect. It's possible that might be the case.

Q I wanted to talk a little bit more about the CV that you provided. We talked about some of the articles that are published. I do note that between 2001 and 2004 you were the founder and I guess either the chair of the board or a board member of a small pharmaceutical startup in the research triangle area, is that right?

A That's correct.

Q And this is DarPharma?

A Right.

Q From looking at some of the work that DarPharma has done, it seems that the D_1 receptor is the primary focus of the entrepreneurial work and research you're doing, is that fair?

A That was correct.

Q And I should say past tense because I guess DarPharma got sold in 2005 to a medical device company?

A That's correct.

Q Are you with DarPharma anymore?

A DarPharma was sold. I have no connection with that company.

Q And does that company exist anymore?

A I think it does.

Q As part of BioValve?

A Well, that's right. DarPharma was bought and become part of another company.

Q Now, during the time that you were working at DarPharma, your focus was on the D_1 receptor?

A That's correct.

Q I imagine this is to get therapeutic products. As I understand it, dopamine is important in the brain, but if you're deficient in dopamine, it's a problem therapeutically because dopamine itself as a whole molecule can't cross the blood-brain

barrier, is that correct?

A Dopamine cannot cross the blood-brain barrier, and CNS diseases involve deficits of dopamine transmission, but sometimes they involve excesses of dopamine transmission.

Q Right. So if you have a disease in the brain that involves a deficiency, and you can't get dopamine into the brain, you have to have a different strategy, and I guess the one you were talking about earlier in your slides, sort of the end of your slides. It begins with an L, levodopa.

A Yes.

Q Now, levodopa is an intermediary product for dopamine synthesis in the brain. Is that correct?

A That is correct.

Q So the idea is if you can get levodopa into somebody, it crosses the blood-brain barrier, and it can then at least theoretically, and it sounds like therapeutically, increase dopamine levels, correct?

A That's correct.

Q You can also do something called an agonist. You can develop an agonist that fools the receptor to make it think that it's picking up dopamine, right?

A That's correct.

Q And so with the agonist, you can up regulate

at the D_1 site whatever the activity the dopamine would be up regulating if dopamine was actually there?

A That's correct.

Q You developed a line of products that you hoped to be able to bring to market from I guess the last 1990s up until 2004, correct?

A That's correct.

Q There was one product that I think was used, if I have my notes here, dihydrexidine. Am I pronouncing that correctly?

A Very good.

Q All right. Dihydrexidine is D_1 agonist, correct?

A Yes.

Q And I should be more precise. It would be a D_1 receptor agonist?

A Well, when one says D_1 agonist, it's automatically assumed it's receptor agonist.

Q And the fewer words I can use on these issues, the better, so I appreciate that.

A Right.

Q So you were developing it for use in Parkinson's disease, correct, in the mid-1990s?

A Well, actually we had several. The neuroscience community had identified a couple of

different conditions where D_1 agonists might be useful. The one that we thought was easiest to test was in Parkinson's disease, but the work of an elegant group of researchers at Yale had also suggested that D_1 agonist would actually be very useful in improving cognition and might even be useful in things like autism or ADHD.

Q Yes, but we'll talk about those in a second, but I wanted to first focus on the Parkinson's component because you published I think it was four papers perhaps in like '93 into '98 talking about this particular agonist, correct?

A Yes.

Q And then in 1998, a group of researchers came out, and guess they've done some clinical work and said that there was a marginal therapeutic window for this drug, and even these marginal benefits might not have even been related to the D_1 receptor stimulation. Do you remember that? It was the Blanchett?

A They didn't say that. Actually, in their study the compound was limited by having to be delivered at a high rate intravenously, and it caused a dramatic drop in blood pressure, but in fact they did associate it in one patient with a very dramatic

improvement. The problem with the study was that the compound causes side effects, which made it unsuitable as an anti-Parkinson's drug.

Q But again, a marginal therapeutic window, correct?

A Right. It had a marginal therapeutic index, correct.

Q And that was the end of your work, or that was the end as far as I can tell on anybody publishing on that particular agonist in that application?

A No, sir, that's not true, and in fact because of the other indication I mentioned, such as cognition, this group at Yale showed that you need much lower blood concentrations, much lower levels of drug at the receptors to get cognitive benefits, and in fact it was hypothesized that this compound, despite the limitations of having to push it fast to get any Parkinson's effects might be useful to test that hypothesis in humans.

In fact, last year two papers were published in schizophrenic patients where this was an add-on to their studies, and in fact there's now I think three other National Institutes of Health studies using that compound as the test for cognition. This is not going to be a proof of principal as opposed to a drug, but

it's the only D_1 agonist that's available for use in humans experimentally, so even though it's not ever going to be a commercial product, it's a very important research tool still.

Q But for Parkinson's then in terms of your perspective, it never went further than this particular application?

A That's right. For Parkinson's disease, it clearly does not have appropriate pharmacokinetic properties.

Q Right. Is this the same compound in the work with schizophrenics, DAR0100?

A Right. That was the number that the company had given it, so they retained that number in some of those publications, but it's still dihydrexidine.

Q In any of these applications, did the pharmaceutical companies that you were attempting to market your therapeutics for, did any of these purchase these and end up producing them and marketing them?

A Dihydrexidine was shied away from by the major pharmaceutical companies because of its pharmacokinetic issues. We had a license agreement for a second generation compound with pharmaceutical companies, and in fact one of those compounds which

doesn't have the pharmacokinetic problems that dihydrexidine does fail toxicology, but as you may or may not be aware, drug development is a very, very expensive and time-consuming area.

We're still interested, and I think the field is still interested, but our compounds have not yet made it into the clinical clearly.

Q They've not made it into the lot --

A Into the clinic as drugs. They're just research tools.

Q Okay. I guess Bristol-Myers Squibb took a look at this, at some of your products and declined to license and produce and market them?

A No. They actually licensed them for a period of time, but then they felt that there was a toxicological problem with one of the compounds, and they gave up the license, so they did spend several years actually pursuing the compounds.

Q I wanted to talk about some of the federal research funding that you describe in your CV. This is on page 3 of your vitae. Now, the first one talks about, and I'm just trying to get an understanding of how this works into the work you're doing now because my understanding is you have a new for profit, privately held pharmaceutical company that you're

involved with, correct?

A Yes.

Q And in this first grant, there's the 2007 to 2012, it has a note there that there's 25 percent effort. What does that mean?

A As I mentioned in response to one of the questions from Ms. Babcock, we in academia have job descriptions if you will, and my job description as a research professor is to spend about two-thirds of my time doing basic research. We are expected to try and support ourselves in that work, though in my case my salary is guaranteed anyway.

What one does is when one requests extramural funding, as I think was talked about with Dr. Deth, for one's research along with that the amount of time that one would spend on a project, the university is to be compensated for that because that's freeing you up to focus on that research problem, so we are required to keep track of this percent effort.

We're not allowed to have more than 100 percent effort totally, and when we prepare our budgets for contracting organizations, whether it be the National Institutes for Health or a foundation or whatever, we have to tell them how we're spending our

time so they know what they're getting of us.

Q And so you've the two that are from 2007 to 2012, so I'm assuming that means that the money is actively coming in on those grants, correct?

A That's correct.

Q And then the third one it notes, and this just maybe a reflection of when you last updated the CV, and again it's not meant to be a tricky question, but I just want to be clear. It says 12-31-07 was the end date, so it this grant currently over?

A It's on what's called a no-cost extension, but essentially this was a pilot grant, and Dr. Goddard and I are actually writing up a series of papers, and we're going to submit this into a larger grant that we'll be submitting sometime later this year.

Q Then the whole category -- I shouldn't say whole category. It's two grants in the category of Pending. What do you mean by pending? What does that status mean as you describe it?

A That means an application has been sent in to a funding agency, and the grant is somewhere in the review process, but a decision has not yet been made that it will be funded or will not be funded.

Q And then that would be somewhat the same if

we go to page 4 for To Be Submitted, so these have not even been submitted to the funder?

A That's correct.

Q To the granting agency yet?

A That's correct.

Q All right. So right now, the ongoing federal research funding you have is expressed in the very first two grants that we see on the CV?

A That's right.

Q Okay. I did want to look just really quickly at Dr. Deth's slide presentation and just put one slide up and ask you a couple of questions about it, and this would have been Petitioners' Trial Exhibit No. 3, and it is Slide 8. It's the mystery slide. It will be there soon.

A I have no disagreement with you.

Q And indicating that you were perhaps anticipating my question, I do want you to take a look at this particular slide, which is page 8 of Petitioners' Trial Exhibit No. 3. If you look at the lower left quadrant there, there is a box, sort of a closed loop, and the reason I don't say loop right off the bat is that it's not circular. It's illustrated as a box, and to orient everybody, this is the one that says phospholipid methylation, correct? Do you

see where I'm talking about, the whole cycle?

A Yes, I do. Yes.

Q Now, Dr. Deth described this as a cartoon or a graphic representation of the normal redox status, correct?

A Yes.

Q If you look at that lower left quadrant that involves dopamine and phospholipid methylation, would you agree that representation is accurate?

A I do not believe that there is adequate data in the literature to support this scheme. It could be hypothesized, and I think it's something that one might wish to test further, but the only literature I'm aware of related to D_4 receptor are a series of I guess three papers or two prior papers from Dr. Deth's laboratory, and I don't believe those papers contain adequate information to justify believing this whole cycle exists. It may or it may not, but I don't believe that adequate experiments have yet been done.

Q Are you aware of any experiments that have been done looking at the question of whether that cycle exists that has concluded it does not exist?

A Well, maybe I can answer that in two ways. The first point I didn't make when I talked about how important this scientific method is is something

that's also not commonly understood, and that is you can never prove a negative because it requires an infinite amount of experimentation to prove a negative because there's always another experiment you can do to try and show that something doesn't happen.

Part of what you were asking me is can you prove a negative, and the answer is that's not our job as scientists. Our job as scientists is to take a hypothesis and try and disprove it. Now, this could be a very good hypothesis, but I do not believe that Dr. Deth has generated adequate data to state that it really does exist and could even be called resembling a theory, and to my knowledge no one else in the literature with the D_4 receptor has ever attempted to replicate his work.

For that reason, it's a plausible hypothesis, but the data in support of it is certainly very, very minimal.

Q Now, you talked a little while ago, and I'm jumping around a bit, but when you described DarPharma, you did mention that you were looking at possible cognitive benefits that might accrue, and we can pull that slide down, in the realm of ADD, autism-like conditions that you were examining as a possible application of the D_1 agonists?

A Let met put this in order of priority. There is good experimental evidence to support the hypothesis that the right level of D_1 activation will improve cognition. There is studies in the rat, in the mouse and in monkeys to show that if you have aged monkeys, for example, who have causative deficits, low doses of D_1 like dihydrexidine will improve their cognition, and dihydrexidine and like some of the drugs will actually help at low doses the cognition in young monkeys.

There's experimental data to test that idea. The clinical studies I describe with dihydrexidine were aimed at translating that finding. When one looks at what D1 receptors do, one can make a speculative leap that it might be useful in autism or ADHD, and obviously if one got a drug into the clinic, one could test that, but there is no data, for example, to show that D1 agonists might work in autism because I don't believe there's a monkey or rat or mouse model that's predictive of autism.

The cognition studies can be done in both rats and mice because there are validated models, so I said that's the speculation that we and others have had, but there's no data whatsoever for that.

Q Did you or any of the partners that you had

in DarPharma ever develop anything to the point for clinical testing that it tested whether a D_1 agonist could be effective in improving any of the symptoms of autism?

A No.

Q Did you ever get projects that were designed to get to a clinical end point for therapeutic end points that were ended before then?

A Well, I don't know how well you're aware of the drug discovery and development timeline, but when one believes that one has identified a candidate that might be useful, there's this long, very expensive period when one has to do very clearly defined safety toxicology pharmacokinetic studies before one is even allowed to give a compound to humans, and what I am is a basic scientist.

I am interested in receptor function and drug discovery. The reason DarPharma was started was we thought we had molecules that would be important as clinical research tools and potentially as drugs, and for a variety of reasons, large pharmaceutical companies didn't have an interest in them because they were injectable-only compounds. Large pharmaceutical companies don't have the scientific fervor that academic researchers do.

They want a pill that you can give to somebody, so we started DarPharma because we thought it would be scientifically valuable to test these ideas if one could get a drug approved for human testing and that there was a market for an injectable drug, specifically for Parkinson's disease because there's already an injectable drug that's used in late-stage Parkinson's disease, and we thought we could do better, so that was sort of if I've covered a lot of ground why we did things.

The goal there was to develop a compound that could test these ideas in people, and we got investors to believe it could also generate money for them if in fact the ideas were correct and the drug passed safety testing.

Q Now, despite the fact that the pharmaceutical company pharmaceutical companies did not get interested enough to purchase these, and you haven't been able to bring one to market, do you still sitting here today believe that D_1 agonists might have a role in improving the symptoms of people with autism?

A As I mentioned, that's a speculation that one could have, and as I also mentioned, it's an intriguing hypothesis with no testing yet done and no

easy way to do that certainly in people for a long period of time, and I don't know of an animal model I could use, but I do think that in terms of both Parkinson's disease and cognition, the D_1 agonists still have potential value.

I'm still very interested in both my work and anybody else's work in the world who could get a compound like that into the clinic. I think it would be a fabulous thing for patients and also for research.

Q And even beyond this one specific family, the D_1-like family of dopamine receptors, is it also your belief that that there may be agonists out there that would mimic the dopamine at the receptor site that might be useful at other receptor sites, whether it's D2, D3, D4, D5 to help treat the symptoms of autism?

A I think potentially, but then again I think we would view it as some autistic patients might respond well to certain types of drugs that might be improvements of the current things that are available, but that's again totally speculation, and if one didn't believe that kind of stuff, one would stop working. One has to have a view that one's work has meaning.

Q And by continuing to work on this again, the idea is that it is possible that dopamine and dopamine mechanisms in the brain might be involved in autism, but I'm not talking about causation but just as a therapeutic intervention that could make a difference in autistic outcomes?

A In my cartoon of the brain I showed the Court, dopamine innervates and has important modulatory for effects in certain parts of the brain. It might be that those parts of the brain are things that have abnormal function in autism, and it might be that if one had a drug of a certain type that affected one or more of the dopamine receptors in those areas, you might get therapeutic benefit.

If I thought that autism was the only target for our drug, I probably would pick another target because I think it's a very, very high-risk type of thing.

My hope would be is that if we could get a drug approved for Parkinson's disease or schizophrenia or something, obviously what happens in the field of neuropharmacology clinically is when you get a compound to prove, if it's safe, people will try it in other conditions where they don't have good therapies, simply because you'd have nothing better to do. I

would expect that autism would be one of the things if we ever got a drug approved that that would happen, and we're not the only people interested in new drugs.

There's a class of compounds called metabotropic glutamate receptor antagonists, and there's a great deal of interest in the autism community about some of the drugs in that class that are moving along with no more information than we have. Because those drugs will be clinically available, I'm sure they're going to get tested in autistic populations.

Q Now, that drug you just mentioned, it's a glutamate receptor antagonist, is that correct?

A Right.

A So the idea would be that if you had excess glutamate in the brain, you would be looking for a way to prevent other neurons from taking that up, so if you had an antagonist, it would prevent the glutamate from being taken up by the neurons, correct?

A No, not actually. I really don't think the Court wants to go here, but glutamate receptors exist in two families, and those two families are ones called ion channel family, and the other are like dopamine receptors, and there are many, many subtypes of each of those receptors, and each of those subtypes

have very important roles that have been worked out by hundreds of scientists throughout the world.

It's a very specific type of compound, and it's not a simple type of mechanism, so it's been targeted for other kinds of illnesses, and I think some people believe well, maybe it might be useful in terms of autism, but again it's pure speculation, and I think what will happen is if the drug gets into clinical use, it will then be available for trial. There's no molecular mechanism that suggests it's going to work.

Q Right. So you describe it as very speculative, but you also described it just a moment ago as an exciting new area that merits further research and that there's a lot of excitement around it involving the glutamate?

A Central nervous disorders seldom have a singular molecular cause. What you're trying often to do is treat them symptomatically. If you have a condition where the symptomatic treatment that you currently have is not very good, you try anything. In Parkinson's disease, we probably have the best symptomatic treatment of any disorder. In other conditions, schizophrenia cognition and whatever, the drugs we have either have lots of side effects, or

they have very limited therapeutic efficacy.

Therefore, if a new compound is available, it's safe, people will tend to try it simply because you get knowledge from doing that and maybe something will work, but you have to be very, very careful about saying that because we think a D_1 agonist or another thing I mentioned that are functionally selected drugs or a metabotropic glutamate line, because you try them doesn't necessarily mean there's any evidence that suggests it's related to the etiology of the disease. You're just hoping it may work for therapy.

MR. POWERS: I have no further questions.

SPECIAL MASTER VOWELL: Any redirect, Ms. Babcock?

MS. BABCOCK: Just one moment.

SPECIAL MASTER VOWELL: Certainly.

MS. BABCOCK: Nothing further. Thank you.

SPECIAL MASTER VOWELL: Any questions from my colleagues? I have no questions for your, Dr. Mailman. Thank you very much.

THE WITNESS: Thank you.

(Witness excused.)

SPECIAL MASTER VOWELL: We've reached the end of our proposed witness list today at 4:41. This may be a record so far in the case. What we would

like to inquire on behalf of my colleagues and myself is have the parties thought any more about their position regarding our rebuttal evidence and the July continuation of these proceedings. Mr. Powers?

MR. POWERS: Thank you, Special Master. Our position remains essentially the same that we would strongly urge that we do all the rebuttal at once, and I think particular today you've seen that the Respondent's evidence and testimony on toxicology, just on the toxicology, is now being split. We have Dr. Brent now and then Drs. Magos and Clarkson later.

To the extent that there are overlaps and intersections between the testimony, between the scientific literature that they're discussing, treating that as one whole unit and not trying to divide it and create a false distinction between the toxicology through Dr. Brent and here, this neatly cabin box.

Rebut on that in a week and a half, and then come back and assume that Drs. Magos and Clarkson are talking about new things or different things just doesn't seem to fit with let's just get the comprehensive case from Respondent and then come back and deal with all of that evidence at one time. Again, for case-specific, we still are absolutely

committed to doing case specific rebuttal before we leave here on Friday the 29th or the 30th, whatever that date is.

SPECIAL MASTER VOWELL: By "case-specific rebuttal," you would mean testimony regarding the specific two children involved in today's case?

MR. POWERS: Yes, Special Master, that's correct whether it's video, medical records, Dr. Rust, case specific comments, anything like that.

SPECIAL MASTER VOWELL: Respondent? Mr. Matanoski?

MR. MATANOSKI: Thank you. Perhaps Mr. Powers misunderstood Respondent's position, which was simply that the rebuttal to the extent it comes then in July would be about toxicological matters, so in that regard, it would be from their toxicologist, Dr. Aposhian.

Now, if Dr. Aposhian want's to wait until July to put together his rebuttal to Dr. Brent as well any potential rebuttal he may have to Drs. Clarkson and Magos, that's not beyond what Respondent believed that's the procedure the Court had in mind in the first place. However, we understand Mr. Powers to be arguing for something far different.

We understand him to be arguing for his

rebuttal on the general case of causation in its entirety, all aspects of it be withheld until July at the time when we take only the two remaining toxicologists. That procedure was far different from the one that Respondent had believed we were heading into in this proceeding.

Respondent's agreement to allow the late addition of an entirely new theory of causation was under the sole notion that we would end our discussions about that with the exception of the two toxicologists at this end of this three-week trial. All rebuttal with respect to that would come in at that time. Now, Respondent has been scrambling as I mentioned for three weeks to respond to an entirely new theory.

What vaccine cases, and we've all sat on them now, has Respondent been presented with the expert's theory three weeks before trial in a single case let alone one that affects 5,000? Now, we've done our best, and we've put up with on Monday and Tuesday of last week experts testifying in far different fashion from their expert testimony as presented in their expert report.

Now, if we're going to extend these proceedings to rebuttal on all these matters,

Respondent may, as we suggested before, we'd have to see what we would do with respect to Dr. Kinsbourne's new theory, we may withhold or ask the Court's permission to do that, withhold for the rest of this proceeding any discussion that we have on this second theory until we had such time to properly prepare for it.

If this is going on all the way out into the summer, we want to have the time then to properly prepare our case for it.

SPECIAL MASTER VOWELL: Let me make sure I understand what you're asking for, Mr. Matanoski, and that is if we allow Dr. Aposhian and Dr. Kinsbourne to testify in rebuttal into July, you're asking leave of Court to present additional evidence on Respondent's case directed toward Dr. Kinsbourne's late-filed theory?

MR. MATANOSKI: That's correct, ma'am. In other words, Respondent's case in chief with respect to responding to Petitioners' theory would not be done at this time, not just in the matters of toxicology, but in the matters of neurology in particular.

SPECIAL MASTER VOWELL: Mr. Powers?

MR. POWERS: And quite frankly we would not object to that. Our position is that these issues are

far too important. If Respondent feels that they need additional time to develop the evidence and develop the testimony on what we think are critical and huge issues here, we don't object. If it's a condition of doing one rebuttal later from our perspective to have additional evidence come in and additional testimony on Dr. Kinsbourne, then we do not object.

SPECIAL MASTER VOWELL: With the understanding that you would then proceed directly into rebuttal.

MR. POWERS: On every.

SPECIAL MASTER VOWELL: On everything.

MR. POWERS: On everything. We do not object to that.

SPECIAL MASTER VOWELL: On everything including the non-Dr. Kinsbourne theories?

MR. POWERS: I think so because if we look at it that way, you start bringing in areas that overlap, and parsing out the toxicology from the neuropathology, if they need more time, and they have more to put on, we are not going to object to that. We would rather have the information in front of you than not in front of you.

SPECIAL MASTER VOWELL: Let me raise this issue, and this is a practical one. I think the

reason that all three Special Masters were quite surprised when you proposed presenting rebuttal at the proceeding in July is that we had scheduled Dr. Magos and Dr. Clarkson to testify on Thursday and Friday, which then meant obviously we were going to go into the following week that we had not set aside.

MR. POWERS: And I apologize for that. I think all along I've been just thinking of the calendar for that week, but you are correct. We did narrow it down to Thursday and Friday.

MR. MATANOSKI: Ma'am?

SPECIAL MASTER VOWELL: Mr. Matanoski, it looked like you had something else you wanted to add here?

MR. MATANOSKI: Yes, ma'am. From the beginning when we were first presented with the notion that Dr. Kinsbourne would be coming in with essentially a second theory of causation, the Petitioners' Steering Committee, has essentially been trying to move back this proceeding. They knew they could not put off this three-week proceeding after all this time to get ready for it. They weren't ready to go with their case because they had a late-developed case.

They developed it not as it was originally

presented to this Court the second theory that Dr. Kinsbourne came to the Petitioners' Steering Committee and offered his services. In fact, they went seeking him, and now they've essentially forced a second theory on this case with very little time for the Respondent to get ready for it.

We were ready to go into this trial because we'd all been set up for this, and as I made very clear, my great fear in this, in this late developed theory of causation coming in was that it took us a long time to put together our experts to respond to the first theory, and we are probably not going to have them again.

SPECIAL MASTER VOWELL: Understood. Now let's talk about second and third order effects here. These are two test cases, and eventually we hope Mr. Powers gets his third case in or the Special Masters may do what we have threatened to do all along, which is come up with a third case another way.

If we don't hear the full case that Petitioners have, Dr. Kinsbourne's second theory on the second theory of causation now, and by now I mean this summer, then we are going to hear it at a subsequent time, and then you are going to have to put together a team to respond to it then.

The reason behind the omnibus proceeding as been to develop that general body of causation evidence that we could then look at other cases for that rubric, and here there are specific facts, so we don't have all of the general causation evidence. Are we not going to have to do this again?

MR. MATANOSKI: I understand.

SPECIAL MASTER VOWELL: Whether in the context of an individual case or many individual cases.

MR. MATANOSKI: And if this Court is going to entertain that the rebuttal for the entire case be essentially pushed over except for perhaps fact specific, pushed over to some later date in the summer, then Respondent is likely, and I'll have to go and confer, but we likely withhold at this time any testimony or evidence with respect to the second theory and then try to put that on in that July timeframe so that we have more time to put our case together with respect to this late developed theory.

SPECIAL MASTER VOWELL: All right. How much time do you all need to consider this because we're obviously going to need to consider it as well. You need to make some decisions I would think fairly soon.

MR. MATANOSKI: We'd need to decide that

tonight I believe, yes.

MR. POWERS: Perhaps we can confer with Respondent tomorrow morning and have a conversation before you all take the bench?

SPECIAL MASTER VOWELL: We would like to hear what your final proposals are, your final thoughts before the three of us retire to consider what a decision would be.

MR. MATANOSKI: Should we do that off the record then, ma'am, after proceedings close here today?

SPECIAL MASTER VOWELL: We can close the day. You all can confer, and I think all of us had planned to be here until 5:00 or 6:00, so you can do it in that length of time.

MR. POWERS: We'd be pleased to do that.

SPECIAL MASTER VOWELL: Okay.

MR. MATANOSKI: Thank you.

SPECIAL MASTER VOWELL: Okay. All right. With that, I think we'll adjourn today, and we'll let you all notify us back in chambers somehow that we're ready to proceed.

MR. POWERS: Yes, we will.

MR. MATANOSKI: Thank you.

MR. POWERS: Thank you.

(Whereupon, at 4:52 p.m., the hearing in the above-entitled matter was adjourned, to reconvene on Tuesday, May 20, 2008, at 9:00 a.m.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 03-584V, 03-215V

CASE TITLE: Claims for Vaccine Injuries

HEARING DATE: May 19, 2008

LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Court of Federal Claims.

Date: May 19, 2008

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