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.	)	

CONDENSED TRANSCRIPT WITH KEYWORD INDEX
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Room 402
National Courts Building
717 Madison Place NW
Washington, D.C.

Monday,
May 12, 2008

The parties met, pursuant to notice of the Court, at 10:00 a.m.

BEFORE: HONORABLE GEORGE HASTINGS
HONORABLE PATRICIA CAMPBELL-SMITH
HONORABLE DENISE VOWELL
Special Masters

APPEARANCES:

For the Petitioners:

THOMAS B. POWERS, Esquire
MICHAEL L. WILLIAMS, Esquire
Williams Love O'Leary & Powers, P.C.
977 SW Barnes Road, Suite 450
Portland, Oregon 97225-6681
(503) 295-2924

For the Respondent:

LYNN E. RICCIARDELLA, Esquire
VINCE MATANOSKI, Esquire
LINDA RENZI, Esquire
U.S. Department of Justice
Civil Division
Ben Franklin Station
P.O. Box 146
Washington, D.C. 20044-0146
(202) 616-4356

C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Petitioners:					
Sander Greenland	69	119	--	--	--
Vasken Aposhian	136	242	--	--	--

E X H I B I T S

PETITIONERS' EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
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P R O C E E D I N G S

(10:00 a.m.)

SPECIAL MASTER HASTINGS: Good morning to all. Please be seated.

My name is George Hastings. I'm a Special Master of the U.S. Court of Federal Claims. To my left is Special Master Denise Vowell, to my right is Special Master Patricia Campbell-Smith, and together we would like to welcome you all to a special evidentiary hearing of the United States Court of Federal Claims.

I'll apologize for the scratchy throat this morning. Hopefully I'll be a little better, but that will help me keep my opening statement perhaps a little shorter here this morning.

I want to start by saying that today we are here really for two purposes The first purpose of course of the hearing that we begin today is to hear the claims under the Vaccine Act of two particular children. That's Jordan King and William Mead, two boys who suffer from autism and certain other medical conditions. The first purpose of this hearing then is to determine whether the autism disorders of Jordan King and William Mead and their other related conditions were vaccine caused.

However, there is a second very important purpose of this hearing. That is, Jordan and William are two of about 5,000 children who suffer from autism or similar disorders and who have filed compensation claims under the Vaccine Act. These 5,000 claims have been grouped together in a joint proceeding known as the omnibus autism proceeding.

The committee of attorneys who represent the Petitioners in the omnibus autism proceeding have designated Jordan's and William's cases as two of the test cases in that proceeding. Therefore, in this hearing today and over the next three weeks we will hear not only about Jordan's and William's particular disorders, but also extensive expert testimony concerning the Petitioners' second general causation theory; that is, the general theory that thimerosal-containing vaccines acting alone can directly cause autism or contribute to autism.

As some of you may be aware, last year the Petitioners presented their first general causation theory. In this hearing then the Petitioners present their second theory, which focuses exclusively on the thimerosal-containing vaccines as a possible cause of autism.

These two purposes for the hearing explain

why up here on the bench you see three Special Masters and not just one. All three of us Special Masters are here in order to hear the general causation testimony to be presented during this hearing, and then each of us will apply that general causation evidence to decide a particular individual test case under the Vaccine Act.

I will decide the test case of Jordan King. Special Master Campbell-Smith will decide the case of William Mead. A third individual case was also scheduled to be heard during this trial to be decided by Special Master Vowell, but that family recently chose to withdraw from this particular trial.

Therefore, a third testimony case relating to this theory of causation is in the process of being selected, and Special Master Vowell will hear the individual evidence in that case sometime later this year and then decide that third case, again applying the same general causation evidence developed during this trial.

I want to begin this hearing thus by acknowledging certain very important people who are in the courtroom today: The families of the injured children. With us today we have William Mead's mother, Ms. Shirley, and several members of the Mead

family. We thank you folks for being here with us today. Later this week we will also have members of the King family and other members of the Mead family.

All three of us want to extend our sympathy to all those families. Clearly both these families, as with all of the families of autistic children, have been through some difficult times. They are certainly deserving of sympathy, but they are also deserving of great admiration for the way they have coped with their children's disorders.

We thank these families for generously agreeing to have their cases designated as test cases in the omnibus autism proceeding. Members of each of the two families will be testifying in this hearing later this week. Again, we thank all the King and Mead family members for their participation in this hearing.

We also wish to thank the counsel for both sides who will be presenting your evidence during this hearing. We know that they have worked enormously hard to prepare for this hearing, and we appreciate that hard work. We also thank the expert witnesses who have agreed to testify before us.

We thank the Judges of the Court of Federal Claims for the Federal Circuit who have generously

allowed us to take over one of their courtrooms for the next three weeks. We thank the U.S. Marshals and all the other wonderful employees of both of the Courts housed in this building who have assisted us so well in preparing for and conducting this hearing.

Next we thank all of you here in the courtroom for being here. We welcome all of you again. Finally, we note that a number of people are listening to this hearing at this time by means of telephone conferencing and that a number of other people will listen to the audio portion of this hearing by downloading that audio off the internet. We welcome all of you who may be listening to this hearing by those means as well.

For those of you who will be here or be listening to this hearing for more than just today, we would like to give you a brief roadmap for the proceeding. After today we will begin at 9 a.m. Eastern time each day. We will take a lunch break of about one hour probably sometime around 1 p.m. We will adjourn each day probably sometime around 5 or 6 p.m., but sometimes earlier or sometimes later depending on the witness schedule for the day.

Next, I note that during this hearing the three Special Masters will be taking turns at

presiding over the hearing. During the family testimony specific to the Jordan King case I will preside, and during the family testimony concerning the William Mead case Special Master Campbell-Smith will preside. During the general causation hearing, which is going to be most of the testimony, we will rotate the task between the three of us of presiding.

Finally, I note that all of us here are guests of the Federal Circuit in this courtroom. Please, and this goes for counsel, witnesses, as well as spectators in the courtroom. Please don't consume any food or drinks of any type in this courtroom.

With that, we're ready to start the case. I'll turn first to the Petitioners' counsel, who will present an opening argument on the Petitioners' behalf. Please proceed. Mr. Powers, will it be you?

MR. POWERS: Yes, it will, Special Master.

SPECIAL MASTER HASTINGS: Please go ahead, sir.

MR. POWERS: Thank you, Special Master Hastings and Special Master Campbell-Smith and Vowell. Thanks also to everybody who has joined us live and telephonically and also good morning to counsel for the Department of Justice sitting up here along side us in front of the bar.

My name is Tom Powers. I'm the attorney of record for both Jordan King and William Mead. I'm also, along with Mr. Williams, my law partner and co-counsel at table here, representing the Petitioners Steering Committee. That's the group of attorneys that represent the interests of the 4,800 plus families who have claims in the omnibus and the presentation of the general causation evidence in the test cases that have come before us and in the test cases that are before us today.

Special Master Hastings might have been sharing my notes on opening because I did want to talk about what the hearing is about, and the first two things on my list were the ones that the Special Master identified.

The first, as an attorney, are the ones that are frankly most important to me. Those are the cases of the two clients that came to us seven years ago now to represent them on behalf of their children for the thimerosal mercury-induced injuries that they suffer, for the regressive autism that they believe and we believe and that we think the science supports are related to the appearance of their regressive autism symptoms, so obviously the hearings today and the proceedings today are the beginning of the formal

resolution of the claims of two very important people, Jordan King and William Mead.

It is also important and something that we're very aware of as we take the stand today that we're speaking on behalf of 4,800 other children who have similar claims in the program. This is general causation evidence that all of those families can avail themselves of as they move forward to resolve their individual claims, important claims to every single one of those families.

There is, however, a third purpose of these proceedings, and that is a very important one in terms of public policy and what goes on outside this room and outside the decisions that will be written in these particular cases, and that's a decision about science and a debate about the science because while we have lawyers who are advocating positions, we have experts who are offering opinions on both sides, and those opinions certainly differ, often very strikingly.

Ultimately what this is about is the science, and what this case is about is not the science necessarily of vaccines strictly. That is, the families here are not taking the position that vaccines generally or conceptually are a bad thing.

This is not an antivaccine case that you're going to hear over the next three weeks. This is a case that is focusing specifically on a mercury-based preservative, thimerosal, that at this point in time fortunately is largely a relic of history.

It's a relic of history largely because it was an uncontrolled experiment on a huge population of children, a huge exposure across a large population over a long period of time over a substance that, as you will hear particularly in Mr. Williams' portion of this opening that we'll be dividing, is scientifically supported to be related to the appearance of these symptoms.

Over the last year and particularly in the first round of test cases beginning with the Cedillo case last June, it appears to be the position of the Department of Health and Human Services that these cases are implicitly sending a public message that vaccines might be dangerous and therefore that the message would get out to the public that people should avoid vaccine and immunization rates should drop and that we'll see outbreaks of infectious diseases.

But again we need to focus not on that rhetoric. It's almost like an imaginal line of rhetoric that focuses from the government's side

exclusively on got to be pro vaccine and support immunizations. The guns on the imaginal line are so focused on that message that it's important that the Special Masters and the larger public health community understand that what we're talking about for the next three weeks and in hundreds of these claims is a mercury-based preservative that's no longer out there.

Unfortunately, it still is in the flu vaccine, and most doses of the flu vaccine, and that application of thimerosal quite frankly, based on the science that Mr. Williams is going to describe, that application of thimerosal ought to be in the dustbin and of history as it is in the rightfully scheduled pediatric vaccines.

During the course of the many years that these cases have been litigated, one of the unfortunate consequences of the Department of Health and Human Services' position that they're going to focus their attention on a rigid pro vaccine/pro immunization message and ignore issues around mercury toxicity, mercury exposure and thimerosal exposure is that we've seen a commingling of interest between the pharmaceutical industry and the vaccine manufacturers, the health maintenance organizations and the Department of Health and Human Services.

The consequence of that has been to cut off at the knees the essential scientific inquiry that needs to happen to make informed public health decisions about immunization policy, but, just as important, they've cut off at the knees the opportunity to develop and push out into the public the science that needs to be out there so that people have confidence in the immunization program and have confidence that their vaccines are not only effective, but safe.

There are a number of examples. The Special Masters are familiar with some of these because we've been arguing these issues for years. There is the issue of access to the Vaccine Safety Data Link. It's a large, robust link database that independent researchers can go into and link vaccine exposures to a whole range of health outcomes.

Beginning in 2003, the Petitioners have asked in various settings to get access to data within the Vaccine Safety Data Link. We learned early on that the federal government has outsourced or privatized the management of the Vaccine Safety Data Link, what was designed to be a public resource to generate public information about public health policy. They privatized it and are spending money

paying the trade organization for the health maintenance organizations to sit over and administer the Vaccine Safety Data Link.

The HMOs have refused access to the data link to allow independent researchers to explore some of the possible associations that are at issue in these cases. The government has refused access to external researchers. There's no access at all to outcome data for children after 2000.

In 2005, the Institutes of Medicine had a hearing and issued a report urging better public access and better public utilization of this rich, robust, unique database, and a lot of those policies have not been implemented by the Department of Health and Human Services.

There are studies that have been proposed and haven't been done. We've heard for years now that there was, for example, a study on thimerosal exposed and nonthimerosal exposed children in Italy to look at potential associations between exposed children and unexposed children and health outcomes. We've never seen the study that the federal government supposedly was doing, and four years ago when we took depositions they were saying that those were going to be out in about two years.

We still haven't seen the study that is looking at an association between thimerosal exposure and autism and autism spectrum disorders. It's getting pushed out year after year after year. The science is needed, and the science isn't available.

About a year ago the National Institutes of Environmental Health Sciences convened an expert panel and recommended two very specific studies. One was using the VSD to extend forward in time and in a larger population the study that Dr. Verstraeten did and published in 2003 in *Pediatrics* looking at an association between thimerosal exposure and neurodevelopmental outcome.

That recommended study by the HHS' own entity, own agencies, hasn't been done. There was a recommendation by that expert committee to do a study of twins and siblings and looking at exposures and outcomes. That study hasn't been done.

In 2004, when the IOM was looking at this issue, they asked the pharmaceutical industry simply to provide information that would provide people the pure data on when thimerosal truly was out of the nation's vaccine supply to get an idea of what the exposure was in the pediatric population during that slow phase-out of thimerosal as a preservative that

began in the year 2000. The IOM report said that the pharmaceutical industry would not provide that information.

This is science that needs to be available. It's science that shouldn't be locked up behind the rhetorical position of defending litigation. It's important that the Department of Health and Human Services be less focused on trying to prevail here and more focused on developing the science to build public confidence in vaccines and to have safe vaccines with safe ingredients.

This idea that information isn't accessible continues even within the litigation, however. The Special Masters may know, and this was discussed before the Cedillo hearing publicly, that it took about a year for the Department of Health and Human Services to agree to make these test case hearings generally open to the public.

There was a concession made by the Department of Health and Human Services in a case that we had identified as a potential test case for hearing during this round of general causation proceedings, and the Department of Health and Human Services has taken the position that the details of that concession, the contents of the decision that might

inform how people who have clients from the program evaluate their case and move their case forward and get resolution, they're taking the position that that is confidential and cannot be disclosed publicly. Again, it's a focus on trying to prevail in the litigation and not a focus on good science, safe vaccines and public confidence.

Now, Mr. Williams is going to in a little bit more detail walk everybody through the elements of the Petitioners' theory of general causation, but I'm going to do a very condensed version of that to give the Special Masters and particularly people who are here in person and attending a very quick roadmap to how we will be laying out the case and how the evidence is going to be coming in in this case.

The first point that we're going to make is that neuroinflammation is a hallmark of regressive autism. The second point that we're going to make is that neuroinflammation leads to what Dr. Kinsbourne has called the overactivated brain. Now, neuroinflammation and overactivation in the brain is a model. It's a useful model for explaining the appearance of autistic symptoms and particularly the symptom of regressive autism.

We'll also be putting on evidence that

anything that can trigger neuroinflammation potentially can be a trigger for the symptoms of regressive autism. Specifically we'll be looking at the thimerosal issue and mercury, and we'll put on evidence that inorganic mercury -- this is the $Hg2_2$ or Hg2+. You'll see it written different ways. Inorganic mercury is an agent that can trigger neuroinflammation. Specifically, inorganic mercury from thimerosal accumulates in the human brain. It accumulates and it persists.

You'll also hear evidence that environmental exposures, a number of them are now known to cause or contribute to the appearance of autistic symptoms, and you'll hear evidence that a gene/environment interaction is a likely culprit in many, many cases of autism; that is, the 88 to 90 percent of the cases where there's no single identifiable genetic cause there's a gene/environment interaction that's going on.

What we will conclude through the evidence on general causation is that thimerosal-containing vaccines belong on the list of potential environmental factors. If you have a list of environmental factors that might contribute, thimerosal-containing vaccines belong on that list for consideration whenever one is

evaluating what might have caused regressive autism in a child where all the other known causes have been ruled out through differential diagnosis. Those are the elements of the Petitioners' general theory of causation.

I want to start wrapping up my comments by talking a little bit about the testimony you're going to hear in the two individual cases. So if where we are at the end of general causation is with a new candidate really on the list of candidates for the etiology of regressive autism, you're going to hear evidence that in Jordan King's case and William Mead's case these two boys have that differential that has been performed by their treating doctors, by the expert doctor, Dr. Mumper, who is the expert in treating autistic children who has evaluated the medical records.

What they will tell you is that each of these boys, and these are important facts. Each of these boys developed normally and typically, meeting all of their developmental milestones well into and after their first year of life.

You'll also hear testimony that within the first year of life they received a significant exposure to thimerosal. They received a full round of

pediatric vaccines containing thimerosal, containing mercury before their first year of life. You'll also hear that their symptoms of autism emerged only after that full round of thimerosal had been administered.

Both of these boys have been diagnosed with regressive autism, and regressive autism is really characterized by three key things. This is the testimony that you'll hear. First, I've alluded to there's a period of normal, typical development for at least a year going into the second year with no obvious signs or symptoms of an autism spectrum disorder. Both of these boys, from the testimony in the medical records, meet that criteria.

The second element of regressive autism is that at a point in time they actually lose, and this is where the term regressive comes from. They lose previously acquired skills. They lose the ability to interact socially. They lose the ability sometimes to speak, either losing discrete words or entirely losing the ability to speak, so they regress in terms of the skills they've already developed.

But just as importantly, they develop new symptoms that were never there before, often behavioral symptoms, self-stimulatory behavior or stimming, as you might have seen it referred to in

some of the medical records: Odd facial tics, odd vocalizations, brand new symptoms that weren't there before. So you're presented with a very clear before and after picture, and those are the pictures you're going to see in both of these cases.

Based on that and the standard that you apply here in the vaccine program on causation, Petitioners believe that we will have satisfied our burden of proof by showing a medically reasonable theory of causation that's scientifically supported by the peer reviewed, published scientific literature. It is a logical scientific theory. Every element follows in logical sequence, cause and effect, leading to the appearance of regressive autism.

There's a temporal relationship between the administration of the thimerosal in these vaccines between day one and the end of 12 months and the later appearance of symptoms after 12 months. All of those elements will have met on the proof that I've just described, and based on that both of these boys ought to be entitled to compensation in this program.

But in addition to putting on that evidence, you will hear additional evidence about why we know that each of these boys was particularly susceptible to the environmental insult that they received through

thimerosal injection because certainly not every child who received that same load of shots developed symptoms like Jordan's or like William's or developed symptoms of any problem at all.

That goes back to the gene/environment interaction. A lot of the genetic issues are unknown, but we can see some indirect and circumstantial evidence in the medical records of both boys that first off they have a problem getting mercury out of their body. They cannot excrete mercury and protect their brain from the environmental insult of mercury provided by thimerosal as well as other children can, so you'll see evidence of that.

You'll also see evidence that both boys, particularly in the couple of years after their diagnosis, their systems were undergoing oxidative stress, and that's going to be important evidence to listen to in light of Dr. Deth's testimony that you're going to hear.

We absolutely can see that this is indirect evidence because the direct evidence is not available. Evidence that children have ongoing neuroinflammation in the brain is often only available via autopsy or brain biopsy, and that's obviously not going to happen in these cases. Evidence that inorganic mercury is

actually sequestered in the brain, the same thing. It's generally autopsy and biopsy tissue sampling that is not going to be done and hasn't been done in these cases.

So the evidence is indirect and it is circumstantial, but it is supportive of the general theory of causation and supports awards of compensation for both of the boys here and, as you apply it to other cases down the road and you'll look for similar evidence, when you see evidence in those cases you also apply the general causation evidence here and reach the same conclusion that those cases ought to be resolved with compensation for those particular children too.

Before asking Mr. Williams to talk in a little more detail about causation, I do want to make a brief comment about the tone, frankly, of some of the expert reports that we saw from HHS and some of the attacks on the experts that we have appearing here. I would be remiss if I don't speak up on behalf of the families and the people that are treating them.

There are doctors out there, Dr. Mumper included, who are, quite frankly, pushing the envelope. They're pushing the envelope because the traditional medical establishment has been telling

them there's no known cause. There's no known cure. There's nothing you can do. Cope with it.

These families, as you know from hearing testimony in the other test cases and the testimony you're going to have here, are doing more than cope. They're working hard to recover their kids, and they can only do it with the help of doctors like Mr. Mumper and Dr. Green, who is the treating doctor. He won't be testifying, but you've seen his medical records in Jordan's case and in William's case. These are doctors who are willing to challenge the establishment on behalf of their patients.

I recall in the Cedillo hearing Dr. Wiznitzer, when I asked him on cross-examination if he believed children with autism and regressive autism could be cured and could they recover and how he could explain how some of the kids seemed to get better; not all the way, but at least partway. He said well, they just grow out of it.

This is not something that kids are growing out of. This is something that they are fighting their way back from. Their regressions are something that present a battle. Their allies in their battle are doctors like Dr. Mumper.

Again, I just think it's a shame that the

tone of some of the attacks that get right up against the line that borders on offensive and the disdain that some of the folks involved in the litigation seem to have for people who are putting their necks and their careers on the line to help these kids.

When somebody says well, these were covered kids, that's just anecdotal, not scientifically robust evidence. All of those anecdotes are our clients, so to those, to the attorneys, to the families, it's not an anecdote. It's a child, and it's a child that's made progress of varying degrees, and that's the evidence you'll hear here.

Again, I'm going to turn this over to Mr. Williams. What these hearings are about are about the science, the medicine, the integrity of the vaccine program, a transparent process that builds public confidence in the vaccines and ultimately a safe immunization schedule for all children. Thank you.

SPECIAL MASTER HASTINGS: Thank you, Mr. Powers.

Mr. Williams, please go ahead.

MR. WILLIAMS: Special Masters, counsel, thank you for the opportunity to make this brief opening statement. I'm going to briefly run through the scientific evidence that you're going to hear over

the next three weeks and show you just a handful of articles, what I think are probably the three or four most important studies and articles that you will see again and again throughout these three weeks.

Let me begin by summarizing again what our theory is in this logical sequence of steps from the vaccines with mercury in them to the inflammation in the brain that leads to regressive autism. Thimerosal delivers inorganic mercury to the brain. I'm going to show you an infant monkey study in a minute that was set up to mimic the infant vaccine schedule in this country, and what it established was that inorganic mercury accumulates in the brain of these children.

When that inorganic mercury is in the brain it leads to oxidative stress for two reasons: One, because of the neuroinflammation itself. As these immune cells are activated, they release all kinds of chemicals that cause oxidative stress and make it harder for the brain to function, but in addition we also know some of the mercury, some of this inorganic mercury, accumulates in neurons itself, and when it's in the neurons it directly leads to oxidative stress.

When a neuron is stressed out from too much oxygen -- it doesn't have enough antioxidants available -- it doesn't function correctly. It

doesn't die, but it doesn't work right. This is not something that we've made up here. I'm going to show you right now a paper that is one of the most comprehensive reviews of how neuroinflammation can lead to autism.

This is a paper entitled Autism at the Beginning. It's written by a group of scientists from California who run one of the largest research centers in the world on the neurobiology of autism. Eric Courchesne is the lead author.

At the beginning of this paper he describes a case of regressive autism. He says: Autism begins in many ways. On the second page he describes a case of clearly pure regressive autism, a little girl who develops absolutely normally until she's 14 or 15 months old and then suddenly loses her language skills, loses her social attention skills and, as Mr. Powers describes, starts to develop lots of new symptoms. Thus, autism begins.

He cites literature to show that in one case cited the autism began early, rapid and unmistakable. You could see it before the kid was six months old. That happens in most autistic cases, but then in a small handful of cases you get this kind of sudden regression.

Now, this is a diagram out of the article itself that shows the brain structure, the complexity of the brain at the time a child is born and at one month and at six months and at two years. The thimerosal injections occur in between each one of those pictures. There's a thimerosal injection in these children right after they're born. There's some more between one and six months, and there's some more between six months and two years. The inorganic mercury accumulates all around those cells in these children's brains as time goes on.

Let's go to the quote, Scott.

This is just a description in the paper itself of the diagram that I just showed you. These are actual pathological brain drawings from autopsied children.

Okay. Next slide, Scott. I don't think we need to show that one.

Now, these children also, we know from autopsies of autistic children, get too many neurons in some parts of their brains. The program that's set up to make their brains grow correctly somehow goes awry and they get too many neurons. What this paper explains is how neuroinflammation, this activation of the brain's innate immune system, can lead to too many

neurons.

It's triggered by adverse events that ignite the neuroinflammatory reactions reported by Vargas. Now, they're citing this Vargas paper, which you'll also see. I'm not going to show that to you now, but Vargas is a study from Johns Hopkins of autopsied brains from autistic children that found neuroinflammation in every one of them. Since then, as you'll see, there's been other studies published that have confirmed that.

Next?

This is still from the Courchesne paper. Vargas found evidence of astroglial and microglial activation and neuroinflammation in both the white and gray matter in samples from the cerebellum.

Okay. Next? Next paragraph?

In all three regions there was enlargement of astroglial cell bodies and their processes. Microglial activation -- these are immune cells in the brain -- was present in the cerebellum, in the cerebral cortex and its underlying white matter, and it had pronounced microglial activation with a loss of some neurons.

In some parts of the brain you get too many neurons. In other parts of the brain you get too few.

It's because the programming of how that brain grows that I showed you from the diagram over time. Between birth and two years, the brain grows four times as large as it is when the child is born, just enormous organization and connection and cell growth going on, and if you get inflammation while that's happening it disturbs the whole orchestration.

Now, this is how he explains that neuroinflammation can cause these structural changes, but he not only says it can explain these structural changes. It can explain the functional changes too.

The next paragraph, Scott, I believe has a quote about that.

Excess glial production or activation have the potential to produce any or all of the previously discussed microstructural findings, but also you'll see he talks about here it also could underlie theories of autism based on functional imaging studies, so neuroinflammation from birth to two can cause structural changes in the way the brain is getting organized and connected, and it can also cause functional changes.

Actually, this Johns Hopkins group is now working on ways to try to attack the functional neuroinflammation as a way to potentially cure autism.

Next? Next slide, please.

This paper also goes on to point out that these inflammatory reactions are going to be identified. Some trigger is going to set them off. A chemical pathogen like a measles virus, or you'll hear evidence of other viruses. There are studies that show malaria at the age of two or three can induce autism in children.

You'll hear evidence of lots of postnatal viral infections that can lead to neuroinflammation and autism, as well as chemicals that can do it. I'm going to show you one in a second.

Okay. Let's go on.

Now, we know that inorganic mercury can ignite this neuroinflammatory process because of a series of studies done in Seattle at the University of Washington in the mid 1990s on adult monkeys. You're going to see these studies over and over again. I'm not going to go through them in detail now, but I just want you to see the first page of each one.

This was a whole series of adult monkeys that were given very low doses of methyl mercury, low doses that were intended not to provoke any kind of acute reaction, and then they sacrificed the monkeys at different times over a period of 18 months.

What they found, these studies all together found that methyl mercury will enter the brain. It will then have the methyl group detach and it will form Hg++, this inorganic mercury, and the inorganic mercury accumulates in the brain over time and is trapped there. It doesn't leave.

They estimated the half life of inorganic mercury in the brain of these adult monkeys to be in years, literally in years because it's so bound up with molecules in there and in these neuro microglial cells that it turns them on, but it can't get it out of the brain so it's trapped there.

Let's show the next one, Scott.

This is another. They published five separate papers out of this single study on adult monkeys. This is talking about the changes in the glial cells in one part of the brain of these monkeys.

Next? Next, Scott?

This is the paper where they looked to see whether it was organic mercury or inorganic mercury in the brains of these monkeys, and what they found was that it was inorganic mercury.

Here's another paper from that study where they confirmed that it was inside the glial cells, the astroglial cells and the microglial cells, where the

demethylization took place. In other words, where the inorganic mercury was formed was inside those cells.

Okay. Next one, Scott?

And they also then looked to see if the number of cells changed in the brains of these monkeys, and they found that they did. The microglia -- those are the immune cells where this mercury is trapped -- multiplied and proliferated and became activated and was still activated at the very end of the study after 18 months.

But moreover, they found a decrease in the number of astrocytes, which is another type of glial cell in the brain. The astrocytes provide vital function and support to neurons, and what they found was that as this inorganic mercury accumulated in the brain it not only activated the microglia, but it reduced the number of these supportive astrocytes.

You'll see the details of these studies as we present the evidence and as we cross-examine the defense witnesses next week.

Okay. Next?

So those adult monkey studies establish that the methyl mercury was demethylated, changed to inorganic mercury which was trapped in the brain and which activated neuroinflammation, proving that

inorganic mercury in the brain will activate neuroinflammation.

Now, this same group of researchers got a grant to do this infant monkey study I told you about, and what's very, very important for this proceeding is that one of the authors of this study, this infant monkey study, is Tom Clarkson, who is a defense witness.

Now, he's not going to come this month. Apparently we're going to hear from him in July, but he's a co-author of this paper, which we think is probably the single, central most important paper in the trial. I highlighted his name there so you can see that he was one of the authors of this paper.

Let me summarize quickly what this shows. Yes. Let's go here first. The inorganic form of mercury was readily measured in the brain of the thimerosal-exposed monkeys. They had both infant monkeys they fed methyl mercury to, and they had infant monkeys that they injected thimerosal into.

There's a quote that shows where it simulated the vaccine schedule, Scott. I wanted to show that one for sure. I think it was on the prior page.

SPECIAL MASTER HASTINGS: Just for the

record, this article is the Burbacher 2005 article.

MR. WILLIAMS: Yes. Thank you, Your Honor. I should identify them better for the record.

Now, there's a quote that shows the simulation if I can find it. It's on the first page, Scott, in the right-hand column. Yes. Right here.

The dosages and schedule of the administration of mercury were chosen to be comparable with the current immunization schedule for human newborns, taking into account that the monkeys grow four times as fast. Again, this is a defense expert who wrote this and who helped to design this study.

Now let's go to the chart of the blood. One of the things, the defense reports are full of how rapidly ethyl mercury is cleared from the blood compared to methyl mercury in these children. The same thing happened with the monkeys. This is a chart of the blood levels of mercury after each injection.

You can see that this is in nanograms per milliliter. That's the measure they have chosen. Our experts will explain later how these concentrations are picked, but the point is blood levels are very high after the injection, but then cleared. Within seven days they return almost to baseline.

And then another injection happens. The

blood levels go up. They come back down again in seven days, over and over again until at the end you can see that the mercury from the blood is cleared very fast in these monkeys. The same thing happens with human infants.

However, the inorganic mercury that got into the brain doesn't leave. This is the chart. The purple shows you what happens to the inorganic mercury after each injection. The first injection you get up to about four nanograms per milliliter, but then even though it clears out of the blood it doesn't leave the brain.

The second shot, you get another bump up in inorganic mercury; the third shot another bump; and the fourth shot another bump to where the infant monkeys in these studies at the end of the study had 16 nanograms per milliliter on average in their brains, and the half-life was the same as in the adult monkeys. It didn't change. It's there. It's going to be there for years.

Now, they haven't yet released the data on the activation of the brain cells in this study. That work is being done and it isn't available yet, but we know from the adult monkey studies what inorganic mercury will do, and this is in the same dose level as

the adult monkey study. Let me show you that quote.

Scott, it's the one that says: Five years. It's on the right-hand side of this. Yes, that's it right there.

The effects of the adult monkeys, and this is Dr. Clarkson again endorsing the validity of those five adult monkey studies that I showed you to begin with, saying that the effects of the adult monkeys were associated with brain inorganic levels only five times higher -- only five times higher -- than in the infant monkeys.

You're going to hear I think lots of studies that show the developing brain, the developing infant brain, is probably 10 times more sensitive to the effects of mercury than the adult brain, and yet we only have a difference of five times here between the measured levels of inorganic mercury in these brains.

Dr. Clarkson also endorses the general nature of our theory.

Scott, if you look at the last thing here?

This article notes, referring again to the Vargas autopsy study: It is important to note that an active neuroinflammatory process has been demonstrated in the brains of autistic patients, including a marked activation of microglia.

So these authors put all this together in the way that I've been trying to explain to you to say that inorganic mercury is delivered to the brain with these injections of thimerosal. It accumulates in the brain and it activates microglia, and if you activate the immune system in the brain with neuroinflammation you can cause regressive autism.

Okay. Next, Scott?

I'm not going to take the time now to show you these autopsy studies, but since the Vargas study was published in 2005 there was another study on autopsies of autistic children published this last year, Lopez-Hurtado, which found exactly the same thing. They found neuroinflammation in all the brains of these autistic children.

And then recently, literally recently -- in fact, one study was just published this week -- an autopsy study of children with autism that found again neuroinflammation, which seems to be the hallmark of the autistic brain.

Next slide?

Now let me say something about epidemiology. The defense reports are full of citations to the various epidemiology studies that have been done in Europe and elsewhere on thimerosal and vaccines and

whether there's been some change in the rate of autism.

We're going to have Dr. Greenland here soon to explain this in great detail, but not one of these studies has ever looked at regressive autism. There's going to be some dispute about what percentage of autistic children in the grand spectrum are truly regressive, but the general consensus I think you're going to hear is it's 15 percent or less.

What Dr. Greenland will explain to you is that it's 15 percent or less of the cases, and you're looking at all cases of autism. You can't see a change in regressive autism in these studies. The studies are just simply uninformative on the question of whether thimerosal vaccines are related to regressive autism.

There is no published case control study on regressive autism. There's no cohort study on regressive autism. As I've just explained, none of the ecologic studies that look at patterns and trends have ever looked at regressive autism.

Now, there are a number of environmental toxins that are going on the list of possible causes of autism, and one of the more recent ones is a drug called Terbutaline. Terbutaline is a drug given to

pregnant mothers to try to stop premature labor so the baby isn't born too preterm. It's not used very much any more because now it's been accepted it causes autism.

It's given in the typically sixth to eighth month, so very late of the second trimester up to the third trimester of pregnancy. There's a case control study that you'll see a lot of later in the trial by Connors, et al. This is the same group, by the way, at Johns Hopkins that did some of the autopsy studies.

Connors, et al. They did a study on twins and siblings, and what they found was that if there was an autistic child and his twin or sibling was given Terbutaline, they were two to four times as likely to get autism as the twins or siblings of autistic children who weren't exposed to Terbutaline.

So that has now put Terbutaline on the list of toxic agents that can cause autism. Guess what mechanism they've now figured out Terbutaline uses to cause autism? It's neuroinflammation. The same group again did an animal study on Terbutaline trying to figure out what is it about Terbutaline that can lead to autism, and what they found is it caused this same type of neuroinflammation and it caused behavioral changes in these rodents.

You'll see that in detail, but here's an example of another agent that's known to cause autism late in pregnancy, near the time of birth, and causes it through the neuroinflammatory process.

Okay. Next slide?

Let me run through just really quickly more for the audience than for the Special Masters who our experts are going to be. We're going to have Sander Greenland, our epidemiologist; Vasken Aposhian, whom you've seen before who is a toxicologist; Dr. Richard Deth, who is a research pharmacist; Marcel Kinsbourne, whom you know, a pediatric neurologist; and then Dr. Elizabeth Mumper, a pediatrician who runs a clinic that treats hundreds and hundreds of autistic children.

Let me just summarize quickly. Marcel Kinsbourne, as you probably know, is the author of the chapter on childhood neurodevelopmental disorders, including autism, in this book, which is the leading textbook of pediatric neurology in the country. In all seven editions of this book, he's been the author of that chapter.

Dr. Greenland is the co-author of this book, which is the leading textbook on epidemiology methods taught in graduate schools around the country. This

is the second edition of the book. The third edition just came out and I won't have a copy until tomorrow, but again we have one of the leading textbook authors on the subject who's coming here to address you.

Dr. Aposhian is a world-recognized authority on toxicology that you've heard of many times before. Dr. Deth has performed and published many of his own studies on thimerosal and neurons and how thimerosal can lead to oxidative stress. And then finally Dr. Mumper is the medical director for the Autism and Research Institute and manages a large clinic that treats autistic children.

Now, there's a debate between the sides here as to whether autism is totally genetic or whether there has been an increase in the rate of autism over the last many years. I think we will be able to convince you that the epidemic is real, that the increase is real.

First of all, there's no such thing as a genetic epidemic. If autism was all genetic, you wouldn't see a change in rates. You can only see an increase if something is triggering it, so it's an interaction between the environment and the genetic susceptibilities of these children.

There's been no change in the criteria for

regression. The defense experts all try to say well, it's just an expansion of the criteria for diagnosis or it's just better ascertainment of the cases. We really don't have an increase in autism. We just have a better awareness of it and are better able to diagnosis it.

That doesn't make sense for regressive autism because a true regressive autistic case is so dramatic nobody would miss it. It's not like they could have overlooked hundreds and hundreds of regressive autistic cases over the last 20 years.

And yet the percentage of autistic cases that are regressive has not changed. It's really pretty much stayed the same over 20 years, which means the regressive cases have increased, but if the regressive cases have increased, that has to be a real increase. They couldn't possibly have missed regressive cases.

So there is genetic susceptibility. Obviously we know there's a genetic component to your susceptibility to the autism spectrum disorder. We know that several environmental factors have already been identified as triggers of autism, and even Respondent's scientists will acknowledge that some of these environmental factors are triggers. Some

viruses are triggers. Some drug agents like Terbutaline are triggers. I already actually went through the Terbutaline example so I won't go through it again.

Another very important concept is in every study of mercury disposition in animals, in rodents, in primates and in humans there is always a wide individual variation in how much mercury gets out of the blood, how much mercury goes into the brain. If you're injecting several million kids with the same level of mercury, you're going to have a wide distribution of effects. Some kids can clear it very quickly and some kids can't.

We believe it's the kids who are at the high end of the curve who are the ones that have the most trouble clearing mercury, and we know from all the studies that there's always some animals or some humans that are in that category. Those are the ones that are at most danger of having the inorganic mercury trapped in the brain in higher quantities and causing this neuroinflammatory process.

Okay, Scott.

And then there's another reason why some children are especially vulnerable. At birth there's a wide variability in how mature the liver is at

clearing mercury. Some kids are born with a much more mature biliary functioning system than others.

The blood-brain barrier develops from birth to three, four, six months of age, and it varies tremendously between kids. Some kids have a much better blood-brain barrier when they're born than others.

We know that some kids don't excrete mercury as fast as others. We know some don't detoxify it as fast as others, and we know that some kids don't have the full antioxidant metabolism that's required for healthy neuronal function and so they're at risk for any provocation of stress on the neurons from oxidative stress. In other words, they're equipped to handle some oxidative stress, but they can't handle excess oxidative stress as well as most children can. You're going to see evidence of that.

So we believe you will be convinced when we're done that thimerosal injections during infancy are a substantial contributing cause of neuroinflammation and the resulting symptoms of regressive autism.

And then just one quick note about the legal standard for causation in the program. We know we have to prove a medically plausible theory of

causation, and I believe we're going to do that. We know we have to prove a logical sequence of cause and effect, and I think we're going to be able to do that.

And we of course have to show a temporal relationship between the exposure and the injury. As Mr. Powers explained, these two kids in this case didn't develop any symptoms until after they got this whole range of doses of inorganic mercury.

That's the end of our opening statement. Thank you very much for your attention, and we'll get on with the science.

SPECIAL MASTER HASTINGS: Thank you very much, Mr. Williams.

For the government, did you have an opening statement?

MS. RICCIARDELLA: Yes, we do, sir.

SPECIAL MASTER HASTINGS: Please go ahead.

MS. RICCIARDELLA: Could we also switch the computers, please?

SPECIAL MASTER HASTINGS: Ms. Ricciardella, please go ahead when you're ready.

MS. RICCIARDELLA: Thank you. Good morning. My name is Lynn Ricciardella, and I, along with my colleagues at the Department of Justice, represent the United States.

Special Masters, I've been working on the autism omnibus litigation for the Department of Justice for over four years, and during that time I have looked at hundreds of pages of medical records in my autism cases, as have my colleagues here today.

In every case those records tell the same message, and that is how dedicated and loving the parents are to their autistic children. It shows what lengths parents will go to and what sacrifices they will willingly make to help their autistic children.

That recognition extends not just to the parents. In the majority of cases that I've reviewed, the records show that the extended family is also intimately involved in that child's care, so I'd like to take this opportunity to open today with an acknowledgement from all of us at the Department of Justice, along with our colleagues at the Department of Health and Human Services, that we have tremendous respect for the families who have to deal day in and day out with autism and who do so courageously and admirably.

I also want to echo Special Master Hastings' sentiments and especially acknowledge the Mead and the King families for graciously allowing their cases and their children's medical conditions to serve as the

test cases in this litigation. Thank you.

Now, as you are undoubtedly aware, Special Masters, the issue of whether vaccines cause autism has understandably garnered much public attention, and with regard to the cases pending in this Court specifically there has been much discussion and rhetoric espoused in the public by those who have formed a judgment through misinterpretation of the evidence or by ignorance of it.

Respondent, however, has chosen to litigate our case inside the courtroom in the proper context before the three of you who have the extremely important job of deciding these cases. We have decided to litigate our case not with supposition or accusation, but with good, solid, reliable evidence. As we did for Theory 1, we intend to provide you with good, solid, reliable evidence that you can apply not just to these two cases, but to most, if not all, of the pending cases in the omnibus.

Now, what is good, reliable evidence? Well, the United States Supreme Court has already said what it is in Daubert. It's evidence based on research with those who have specific training and experience in the subject matter being discussed. It's hypotheses that have been tested. It's opinions that

rise above the level of pure speculation. It's evidence of research that's been reduced to writing, exposed to the peer review process, scrutinized, discussed and replicated.

It's testimony from experts who have experience in the specific area for which they're testifying, experts who treat autistic children, experts who research autism, who research the behaviors of autism and the neuropathology and the neuroanatomy of autism, experts who research specific types of mercury and experts who actually treat mercury poisoning.

Now, Respondent will present testimony from some of the world's most prominent experts in their field. Unlike Petitioners' experts who broadly speculate about an unlimited universe of scientific possibilities, Respondent's experts root their opinions in decades of meticulous, specialized research.

You'll hear experts from Respondent who are experts in toxicology who each possess their own individual expertise, but who all ground their opinions on the most well-recognized and well-established tenants of toxicology, namely dose, form of exposure and root of exposure. These renown

toxicologists will explain how Petitioners' experts directly and indirectly ignore scientific foundations, replacing scrutinized evidence with novel theories and speculative hypotheses.

You will learn that the mechanisms of damage hypothesized by Respondent's experts have never been validated and are not accepted by the rest of the scientific community. You will hear from neurologists who focus their research on the neuropathology and the neuroanatomy of autism.

However, no one has conclusively found or discovered the neuropathological origins of autism. Each expert will confront that the findings reported in the literature indicate that the pathogenesis of autism arises in the early stages of brain development in utero.

Now, the neuropathology of mercury toxicity has also been studied, and it's not consistent with the findings that have been reported in relation to autism. You will hear that there is no neuropathological evidence whatsoever that thimerosal could injure the brain in a way that would result in autism.

You will hear from the world's experts in the diagnosis, treatment and research of autism. You

will hear from the experts who actually write the criteria that the rest of the world uses to diagnose autism. You will hear from experts who have a particular expertise in regressive autism. They will tell you it's not rare, and there is no evidence whatsoever that there are any biological differences between regressive autism and nonregressive autism.

You will hear from Respondent's experts in epidemiology who will explain that multiple, credible studies have been done in different countries using different methodologies, but they all come to the same conclusion: There is no association between thimerosal-containing vaccines and autism.

Special Masters, it's very important to keep in mind what the issue before the Court is in this litigation. This issue is about thimerosal-containing vaccines administered to children. This issue is not about whether mercury is good or bad. This issue is not about whether any form of mercury is good or bad.

Let's be clear. The allegation levied in this litigation is whether these children developed now we're hearing regressive autism because of exposure to a specific form of mercury by way of a specific route of administration given at specific times and in specific amounts.

Now, as you consider the evidence I'd like you to please keep in mind four essential concepts. The first is what is the substance being discussed? This case is about thimerosal, which is 50 percent ethyl mercury. Now, as Mr. Williams went on at great length, a lot of Petitioners' case is now about inorganic mercury. As you reviewed the Petitioners' expert reports, you saw that a lot of them rely on methyl mercury. This case is about ethyl mercury.

Pay particular attention to the way in which Petitioners' experts conveniently move between the different types of mercury. Well, there are different types of mercury, but none has ever been shown to cause autism.

The second concept I'd like you to keep in mind is dose. This case is about exposure to small quantities of ethyl mercury administered to children at specific times, usually at birth, at two months, at four months and at six months of age. Again, pay close attention to Petitioners' evidence. A lot of it will concern very high dose, continuous exposure to methyl mercury.

Now, nobody here disputes the fact that mercury can be harmful, and nobody here disputes the fact that mercury is a neurotoxin, but Respondent's

experts will explain the importance of dose in assessing the risk of chemicals.

Every substance can be harmful to humans in sufficient doses, including water, salt or oxygen. The dose of thimerosal administered in a routine childhood vaccine, however, is thousands, if not tens of thousands, times smaller than the amounts of thimerosal known to elicit adverse effects in humans.

Now, as we heard a lot during the first theory of causation, the most fundamental tenant of toxicology is that dose makes the poison, and that's why the proper focus of this litigation should not be whether mercury is a neurotoxin. It is. The proper focus of this litigation should be whether ethyl mercury is neurotoxic at the specific levels contained in childhood vaccines.

Now, the third concept to keep in mind is who is the exposed subject? This case concerns human beings, specifically children administered thimerosal-containing vaccines postnatally. This case is not about in vitro studies. Petitioners will rely on in vitro studies performed in petri dishes or studies done in animals, but once again this case concerns humans.

The fourth and final concept I'd like you to

keep in mind is critically important, and that is what is the clinical outcome that's being discussed? This case is about autism. This case is not about the death of snail neurons in a petri dish when thimerosal is placed directly on top of them. This case is not about high doses of methyl mercury that could potentially cause subtle neurological signs and symptoms. This case is about autism.

Special Masters, in the six years since the Court created the omnibus autism proceeding Petitioners' hypothesis has not moved beyond the realm of pure speculation. It was a relatively new hypothesis back in 2002 when the Court created the OAP. It's no longer new.

If you recall, the Petitioners asked that the hearings in these cases be delayed because they said the science was continuing to evolve. They were right. The science did evolve, and this issue has been studied, investigated and tested not just here in the United States, but by the worldwide scientific community, and every time it has been looked at it has been rejected.

Now, Mr. Powers talked this morning about a scientific debate. There is no scientific debate. The debate is over. There's no scientific

controversy. The only controversy is the media controversy, propelled by those groups who were founded on the premise that vaccines cause autism or by those groups who promote and advocate experimental therapies for autism such as chelation. The credible scientific community has already spoken on this issue and has rejected it.

Now, Mr. Powers talked also about the need for this case to be about science. That is absolutely correct, but to appreciate how radical and unscientific Petitioners' hypothesis is it's important to look at the origin of that hypothesis.

Now, where would you think that origin to have originated? Perhaps within medical experts from within the autism community? Logical, but that's not what happened. Perhaps within the toxicological community, experts who specialize in ethyl mercury or who treat mercury poisoning. That's not what happened either.

Would you at least have expected the hypothesis to originate within the medical or scientific community at large? You'd be wrong. Would you ever have expected the hypothesis to originate with a marketing consultant? That's exactly what happened.

There was nothing in the scientific literature until the year 2000 when a woman named Sallie Bernard, who is not a medical professional -- she's a marketing consultant and the mother of an autistic child. She published an article entitled Autism, A Novel Form of Mercury Poisoning. Now, she wrote the article in 2000, but she published it in 2001 in a journal called *Medical Hypotheses*.

Now, this was not a peer reviewed article that appeared in a journal of known repute. Let's take a look at how the journal describes itself. We've taken this directly off of the journal's website. Under the Aims and Scope section it states:

Medical Hypotheses takes a deliberately different approach to review. Most contemporary practice tends to discriminate against radical ideas that conflict with current theory and practice. *Medical Hypotheses* will publish radical ideas so long as they are coherent and clearly expressed.

Special Masters, you heard a lot of testimony during the Cedillo trial and the three trials in Theory 1 how the peer review process is really the bedrock of scientific credibility. Well, the editors at *Medical Hypotheses* don't agree.

Here's what they have to say about the peer

review process: Traditional peer review can oblige authors to distort their true views to satisfy referees and so diminish authorial responsibility and accountability. Instead, the editor of this journal is going to be a chooser, not a changer. In other words, the journal is going to assume that the author is correct rather than have the peer review process assess that credibility and reliability.

That's not all the journal says about the articles that it will publish. It says: Even probably untrue papers may be judged worth publishing if they contain aspects, ideas, perspectives, data that are potentially stimulating to the development of future science. Even probably untrue articles.

There's another section on this website entitled Guide for Authors. It explains that if you want an article published in this journal you have to pay for it. You have to pay a page charge. The papers won't be published until payment is received. So if you want an article published in *Medical Hypotheses* you can. It can be radical, it can be unsubstantiated, and it can probably even be untrue. You just have to pay for it yourself.

Now, when the Bernard article came out in 2001, the groups that had been advocating for a link

between vaccines and autism started to dangerously promote the idea that thimerosal in vaccines was creating an autism epidemic in this country, and thus began their running indictment of the CDC, the CDC's vaccination policies and their continuous accusation against our nation's immunization program.

Because of the enormous public health concern generated by these accusations, the scientific and medical community became involved. In 2001, the Institute of Medicine asked its Immunization Safety Review Committee to look into the issue.

Now, in 2001 the IOM's committee did not just focus its attention on autism. That was one of the outcomes it looked at, but in 2001 they looked at a variety of neurodevelopmental disorders, and here's what the conclusion that the 2001 committee said it stated the evidence was at the time:

That it was inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, ADHD and speech or language delay. The 2001 committee specifically recommended that additional studies be done, particularly epidemiological studies.

Well, the Safety Review Committee of the IOM met again in 2004, on February 9, 2004, and by this

time the issue of thimerosal in vaccines had become highly publicized. They invited the public to address the committee to express its viewpoint. Many of the hypotheses relied upon by Petitioners in this litigation were presented to the IOM in 2004 and rejected by it.

Now, between the time the committee wrote its 2001 report and convened again in 2004, multiple credible studies had been done. As I mentioned before, they all came to the same conclusion: There was no association between thimerosal-containing vaccines and autism.

This time, in 2004 the committee specifically focused on just the neurodevelopmental disorders of autistic spectrum disorders or autism for short. They made a variety of conclusions, and here's what they had to say about causality: The committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism. Now, that was the strongest possible conclusion available to the committee.

They also made a conclusion with regard to the biological mechanisms that underlie this hypothesis, and here's what they said: In the absence of experimental or human evidence that vaccination,

either MMR vaccine or the preservative thimerosal, affects metabolic, developmental, immune or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.

Now, the committee did recommend that further research be done to look into the possible causes of autism. Here's what they said about what that focus of research should be: It should be directed towards those lines of inquiry most supported by the current state of knowledge. The vaccine hypotheses are not currently supported by the evidence.

While the committee strongly supports targeted research that focuses on better understanding the disease of autism, from a public health perspective the committee does not consider a significant investment in studies of the theoretical vaccine/autism connection to be useful at this time.

Special Masters, it's been four years since the IOM came to those conclusions, and in those four years the evidence continues to increase to support that conclusion. As I mentioned earlier, the hypothesis of thimerosal and autism has been studied

and tested, and not just here in the United States. It's been tested by the worldwide scientific community, and the hypothesis has been resoundingly rejected.

The following are just a sample of those scientific organizations that have rejected this hypothesis: The World Health Organization, the Institute of Medicine, the American Academy of Pediatrics, the European Medicines Agency, which comprises 30 member countries, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Canadian Pediatrics Society, the Canadian National Advisory on Immunization. Again, this is just a sample of the many organizations that have rejected this hypothesis.

How did Petitioners' experts deal with the worldwide scientific community against them? They said well, they weren't looking at the right evidence. They argue that the evidence relied upon by the scientific community doesn't apply to a very rare, very small, genetically susceptible subgroup of children who develop regressive autism only as a result of thimerosal-containing vaccines. But that hypothesis is only as reliable and credible as the evidence upon which it is based.

Now, once again this concept is also not new. Mr. Powers talked about government rhetoric to worry about and to keep emphasizing how these cases pending in the omnibus will affect our nation's immunization program. Well, it's not just government rhetoric. The IOM in 2004 was concerned about it too. Here's what they said about this hypothesis of genetic susceptibility:

The benefits of vaccination are proven, and the hypothesis of susceptible population is presently speculative. Using an unsubstantiated hypothesis to question the safety of vaccination and the ethical behavior of those governmental agencies and scientists who advocate for vaccination could lead to widespread rejection of vaccines and inevitable increases in incidences of serious infectious diseases.

Now, having failed to find the validity they need in the scientific community, Petitioners now turn to the legal one. But the first pronouncement that vaccines cause autism should not come from the courtroom. It should come from science.

I'd like to end this morning with the oft cited quotation from the venerable Judge Posner of the Seventh Circuit. He said: The courtroom is not the place for scientific guesswork even of the inspired

sort. Law lags science. It does not lead it.

Special Masters, the scientific community has considered and rejected the allegations before you in this litigation. So too should this Court. Thank you.

SPECIAL MASTER HASTINGS: Thank you, Ms. Ricciardella.

MR. POWERS: Special Master, I know we didn't use the full hour. If we could have a very quick, five minute rebuttal opening?

SPECIAL MASTER HASTINGS: Go ahead.

MR. POWERS: Thank you. Very specifically, I just wanted to address a couple of things because I think it's important to keep some of this in perspective.

The discussion you heard from Respondent on the 2004 IOM. It's important to remember several things about the 2004 IOM. Mr. Williams described and showed to you and you've reviewed in evidence a series of papers, important scientific papers from reputable researchers in peer reviewed, published, indexed scientific and medical journals that were not even considered by the 2004 IOM.

When one looks at the bibliography of the 2004 IOM you won't see, for example, what we've

identified as a critical study -- that's the 2005 Burbacher/Clarkson infant monkey study -- because the study hadn't been done. You won't see cited the Vahter and Charleston papers. Those are the adult monkey studies that Mr. Williams described from the mid 1990s.

You won't see any of that work in the IOM, and in fact the quote from the IOM about the physiological mechanisms that have been examined did not include the neuroinflammatory process. The IOM never saw it because they hadn't been done yet. The brain autopsy studies. They haven't seen the studies that came out in 2005, 2007 and 2008.

We reviewed the Petitioners' master reference list that was submitted to the Court, and approximately 275 of the articles on that list were published after the October 2004 IOM report was issued. The 2004 IOM report was a snapshot in time, and science is not a snapshot. Science is a movie, and it moves forward and moves forward by hypotheses being offered and tested.

The other point I wanted to make is about the difference between speculation and hypothesis because too often Respondent uses those terms interchangeably. When Petitioners are talking about a

hypothesis, we're talking about a hypothesis that means an idea that explains the known facts, an idea that can take a disparate set of facts, organize them in a consistent way and offer an explanation of, in this case, a mechanism that is consistent with the known facts and, just as importantly, can help predict some facts that may come down in the future.

So it is more than speculation. These are hypotheses that are testable. They are subject to studies that use their conclusions as the null hypothesis. They're replicable, and over time they will be replicated if, particularly in the clinical area, money goes into the research.

One can't help but notice with the huge number of expert witnesses that the Respondent has brought into these cases and the tens of thousands, perhaps hundreds of thousands of dollars being spent to bring those witnesses in in the litigation context, is perhaps some of that money could go to support clinical trials and case control, placebo, blinded trials of some of the medical interventions just as an example of public health resources that could be used in a different way outside the litigation to answer scientific questions and to address the health of these kids.

That 2004 IOM, since it's a big part apparently of the Respondent's position, needs to be put in context. I know that in the 2005 infant monkey study that was authored by the lead investigator was Thomas Burbacher at the University of Washington and Dr. Clarkson, who has been identified as Respondent's witness was the co-author on there.

It's important to note towards the end of that study that there's a comment in there about the 2004 IOM. There's a comment that explains the conclusion, the approach the 2004 IOM took: It's difficult to understand, given our current limited knowledge of the toxicokinetics and developmental neurotoxicity of thimerosal, a compound that has been and will be continued to be injected into millions of newborns and infants.

So the credible, reliable, peer reviewed published researchers, including at least one on their side of the case, have identified a weakness in the 2004 IOM. As I said in my opening, you can't cut science off at the knees, and we propose that the 2004 IOM closed the chapter on this issue before the story really started to get told.

The story that you will hear in this hearing, the presentation and the evidence, is a

scientifically sound description about ongoing story, and we don't know what the end is going to be, but we do know that where we are today is that we have a mechanism of injury that meets the standards of causation in this program, and there is medical evidence that these two children satisfy this burden and are entitled to compensation.

SPECIAL MASTER HASTINGS: Thank you, Mr. Powers.

Well, we've heard from attorneys this morning. Are we ready to start with the expert witnesses?

MR. WILLIAMS: I think we are. Dr. Greenland?

SPECIAL MASTER HASTINGS: Dr. Greenland, could you please take the witness chair? Please have a seat, sir. I'll ask you to raise your right hand.

Whereupon,

SANDER GREENLAND

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

SPECIAL MASTER HASTINGS: Please go ahead then, Mr. Williams, when you're ready.

DIRECT EXAMINATION

BY MR. WILLIAMS:

Q Good morning, Dr. Greenland.

A Good morning.

Q Before we go into your qualifications, you prepared a couple slides that just summarize what your general opinion is that you're going to be discussing today?

A I have.

Q Okay. Let's just put up there what your main point is, and if you would just explain it, please?

A Well, the epidemiologic literature has not ruled out the possibility that thimerosal-containing vaccines -- I'm going to call them TCVs -- are associated with a prespecified type of autism of a regressive form.

I want to emphasize that what I'm testifying about is the limitation of the epidemiologic evidence. That's strictly my narrow scope of expertise and the statistics surrounding it.

MR. WILLIAMS: Next slide?

SPECIAL MASTER HASTINGS: Mr. Williams, before we go on to the next slide --

MR. WILLIAMS: Yes?

SPECIAL MASTER HASTINGS: You've got a series of slides that he'll be talking about here?

MR. WILLIAMS: Yes.

SPECIAL MASTER HASTINGS: Do you have paper copies of that presentation?

MR. WILLIAMS: I don't know how many. We only have two right now.

SPECIAL MASTER HASTINGS: All right. Let's mark one of them. What we did in the last trial I think was very helpful. We'll mark these things. This will be Petitioners's Trial Exhibit No. 1.

MR. WILLIAMS: Okay.

SPECIAL MASTER HASTINGS: We'll place them into the record, and then later on if the witnesses and counsel can help to do this as you go from Slide 1 to Slide 2 to Slide 3, if you could mention we're now going to Slide 3. Then later on when we go back and read the transcript we can follow along. It will be much easier to follow the testimony if we have that roadmap.

Let's go ahead and mark that. We'll give a copy later on to the court reporter.

MR. WILLIAMS: Who does the marking?

SPECIAL MASTER HASTINGS: Well, we'll mark it later. We know what this one will be, Petitioners' Trial Exhibit 1.

MR. WILLIAMS: All right.

//

(The document referred to was marked for identification as Petitioners' Exhibit No. 1 and was received in evidence.)

SPECIAL MASTER HASTINGS: Go ahead, Mr. Williams.

BY MR. WILLIAMS:

Q Okay. One more slide about the main points of your testimony, and then we'll go into your qualifications, okay?

A Okay. Well, in published control studies that I have seen, but not analyzed, clearly regressive autism is very uncommon, as the expert, Dr. Fombonne, and we'll get to his calculations, as he said.

Hence, even if the studies had separated the clearly regressive cases, a true association could easily have been missed. They hadn't done that, however.

Q Okay. We're going to go through that in more detail just in a moment, but let's turn to your qualifications if you would, and this is now the fourth slide in the set.

A Okay.

Q I told the Court that you were the co-author of this book. Is that the truth?

A That's correct.

Q Okay. And there's a new edition of this that has just come out?

A That's correct.

Q And is this textbook used around the country and the world?

A It is. It is.

Q And you are an author on over 300 peer reviewed articles?

A That's correct.

Q Okay. Slide 5. Are you a Professor of Epidemiology and Statistics at UCLA?

A Correct.

Q How long have you been there?

A I've been at UCLA on the UCLA faculty since 1979.

Q And are you frequently invited to give talks and presentations around the world on epidemiological methods?

A That's correct. And also statistics.

Q And also statistics. All right. Slide 7. You have a Doctorate in Public Health from UCLA?

A That's correct.

Q So you were there before you started working there?

A That's correct.

Q Explain what these executive committees are and so forth, please.

A Well, Society for Epidemiologic Research is the largest society of epidemiologists in the world today. I've served on the executive committee of that society.

I've also been chair of the Epidemiology Section of the American Statistical Association, which is the largest statistical society in the world today.

Q And then I guess this is coming to Slide 7 next. You've been a consultant in epidemiology and statistics for many different governmental agencies and private corporations?

A That's correct.

Q We don't have the whole list here? There's a lot longer list than this?

A Much longer.

Q And then you've been an investigator yourself on many grants and contracts --

A That's correct.

Q -- for NIH and other prestigious organizations?

A That's correct.

Q And then we're ready for I think Slide 9. Slide 8? Okay. Slide 8.

Again, just some more of your qualifications. You've been a referee for some of these journals. Are these major journals in the field?

A They are.

Q Explain what these two journals are or three journals are in the last section for us.

A Well, *American Journal of Epidemiology* is the most widely circulated, largest journal of epidemiology in the world as far as I know, and *Epidemiology* is maybe number two.

And then *Statistics and Medicine* is one of the biggest medical statistics journals in the world, probably the biggest, and the *European Journal of Epidemiology* is the main journal in Europe on the continent.

Q Okay. Now let's turn to what you've prepared to talk about today. We'll go to what is now Slide 9. Is that right? Okay.

I'll just let you explain this, and I'll interrupt you from time to time if I think there's some clarification that needs to be done.

A Yes. Well, autism, like many other diseases, is largely unknown causation and includes neurologic diseases of adults such as MS and ALS has clinically recognizable subtypes with distinct development trajectories and possibly different etiologies. What it has in common with these diseases is that by and large there is not an accepted mechanism that's been worked out in detail about how these diseases arise.

An association between TCVs and regressive autism, especially clearly regressive autism, would have been seriously diluted in all the available epidemiologic studies, if there were such an association.

Q By diluted, what do you mean by diluted?

A Well, that I hope to clarify in the upcoming slides.

Q Okay.

A The association, if present, would be submerged in the other types.

Q Okay. Let's go to Slide 10. I see. The slides are marked on the screen. They're not marked on my copy. I'll be able to do this better now.

A This says 10 on my screen.

Q Yes, it is Slide 10.

A Right. Should I continue?

Q Yes.

A Well, specificity of an association means that an exposure has little or no association with the majority of types in a disease category, but some association with one or a few of those types.

If a highly specific association is present, failure to separate the types can severely dilute the association of the exposure with the disease category to the point that it can become undetectable.

Q You just can't see it in the numbers, right?

A That's correct.

Q Okay. Slide 11?

A Regressive autism may include cases without early developmental abnormalities. This is acknowledged by quite a bit of the peer reviewed literature and also testimony given in this case by Dr. Fombonne.

Q In his report, right?

A In his report.

Q Right.

A I'm calling them clearly regressive cases simply for lack of a better term. Such cases would be a minority of regressive cases and thus a small minority of all cases of autism, so even if something

called regressive cases is common, but certainly not the majority of cases, then clearly regressive cases would become quite uncommon.

Q And you've gone back to Dr. Fombonne's report and pulled some information out of that that helps to illustrate your point, right?

A That's correct.

Q Okay. Let's look at that.

A Next slide.

Q The next slide. There we go.

SPECIAL MASTER HASTINGS: And now we're on Slide No. 12.

MR. WILLIAMS: Slide 12.

THE WITNESS: Dr. Fombonne argues that regressive autism is common enough to be detectible in available studies. He estimates there it's around 20 percent of cases could get that label.

On the other hand, he cites data that 72 percent of cases of regressive autism are not clearly regressive, so that means that clearly regressive cases are only 20 percent times 72 percent of all cases. That would be six percent of the total.

He calculates that figure and gives it in his report as an upper bound. He actually expresses skepticism that it's that high a percentage.

//

BY MR. WILLIAMS:

Q So he's suggesting that the percentage of clearly regressive cases may be less than six percent of all ASD diagnoses?

A He seems to state it more strongly than that; that he doubts that it's as high as six percent is my impression.

I will say here that not being an expert in Dr. Fombonne's area, I'm relying on his testimony here and the literature he cites, which I've gone back and examined it and it points to.

Q Okay. Let's go to Slide 13.

A Well, to take an example of what I'm talking about with this dilution issue, suppose that TCV is associated with a twofold increase in the risk of clearly regressive autism. I'm just picking that number because it's often chosen as a boundary point. Because it is that number or I'm claiming that or it's more or less, but just to take a number that's often used. It's a nice, round figure.

Suppose that it's not associated with any other type. It's only associated with clearly regressive autism. Suppose also that without TCV exposure the associated type represents only six

percent of the disease category and that the total number of cases in the category would be 100. I'm taking this figure of six percent from Dr. Fombonne's report, and that's the upper bound.

Q Okay. Now we're on Slide 14.

A Then, without the exposure, the number of cases with the associated type would be 100 times .06, 100 times six percent, which is six.

Q So out of 100, you would expect six cases roughly of clearly regressive autism?

A That's correct. That's without the exposure. We're assuming this is without the exposure they're six percent.

With the exposure, however, the number of cases of clearly regressive autism would double to 12 if it doubled the risk.

Q Right.

A And that would be in excess of six cases over the original six.

Q Okay. Let's go on to Slide 15.

A This excess produced by the vaccine would result in a total of 100 plus six or 106 cases, which is only a six percent increase in the overall risk of the disease.

This six percent increase translates to a

risk ratio of only 106 over 100 or 1.06. This corresponds to Dr. Fombonne's upper bound so that if I took a number more in accord with what he seems to express is more likely it would be even less than that 1.06, something even closer to one.

Such a small risk ratio is already beyond detection by epidemiologic studies of autism or of most topics for that matter. Epidemiology is simply too crude a tool to be able to detect -- increases in risk of this order are even closer to one -- except in extraordinarily rare instances.

Q Now we're going to Slide 16.

A Some studies consider more broad categories than autism. Some consider the category of autism spectrum disorder or, even more broadly, developmental disorders. These are some of the studies cited by Dr. Fombonne.

If they're looking at a broader category than general autism then clearly regressive autism would constitute an even smaller percentage of these categories, so an association of TCVs with one of these categories would be diluted even more than in the above examples, which means the risk ratio from this doubling of risk of clearly regressive autism would be even closer to one than that 1.06 we

calculated in the previous slide.

Q And even more difficult to see in any epidemiological studies?

A In that case it would be beyond detection by epidemiologic means.

Q Okay. Next slide, Slide 17?

A If 28 percent of cases of regressive autism are clearly regressive, and this is one minus the 72 percent that Dr. Fombonne cited from his study. The 28 percent remaining are clearly regressive, and TCV effects are limited to the clearly regressive type. A study of TCVs among all regressives would still be unlikely to detect the association.

Time/trend studies of general autism, which have been cited extensively in this situation, would be unable to detect a specific association of TCVs with clearly regressive autism because a diluted association, something as small as I was illustrating, would be submerged by the large background trends reported.

Q Okay. Go to Slide 18.

A Now, genetic factors in regressive autism do not rule out or even argue against TCVs as a cause.

Q Okay. Why not?

A Even when genetic factors must be present

for the disease to occur, they in no way limit the importance of other factors. A classic example is PKU, a genetic disorder which requires presence of dietary phenylalanine to produce mental retardation.

Q And PKU is genetically based?

A It's a genetically based disease. That's well established, and it's also well established that the mental retardation that can arise from it can be prevented by restricting dietary phenylalanine.

Q And that's an example of a postnatal type of brain problem that's caused by an environmental agent, correct?

A That's correct. It's a prenatally determined condition, but it's the postnatal exposure that determines the retardation.

Q All right. Now let's go to Slide 19.

A Now, I feel it's important to discuss this concept of statistical nonsignificance because it arises so much in litigation, as well as in scientific debates, and it seems to be widely misused and misunderstood even by experts.

This is a topic that I and several of my colleagues have lectured about all over the world, a major problem in the scientific literature. Failure to detect an association is what this means,

statistical nonsignificance. It is not a demonstration of no association. It only shows that no association -- I should have put that in quotes, no association -- is one among many possibilities that are compatible with the data.

Now, the compatibility term used there is by conventional and effectively arbitrary standards, but I'm not going to talk about those standards today. I'll just adopt them like everyone else and simply discuss why even following those standards we have to be careful to understand that failure to detect an association is not a demonstration of no association.

Whenever one considers statistical significance or nonsignificance one should ask what other possible levels of association are also nonsignificant. These are given by confidence intervals.

Q Okay. The next slide starts to illustrate these, correct?

A Yes.

Q This is Slide 20. All right.

A So to discuss their relation, suppose a study reports a risk ratio of 1.00, no association observed at all, but with 95 percent confidence limits of .5 and 2.0, so one-half to two.

These limits would indicate that the observed risk ratio is not significantly different at the conventional .05 level from a risk ratio as small as .5 or as large as two. That means that all the values within this range would not be rejected by the same statistical test that did not reject the 1.0. No association, and so in effect using this standard they would all still be in the running according to this criterion.

Q Just because the relative risk nominally comes out at 1.0 or even 1.2, if the confidence intervals are much wider than that there could be other values if you did the study again?

A They wouldn't even have to be much wider. What one needs to understand very carefully about epidemiologic studies and statistical studies of that sort is that they leave open a broad range of uncertainty. They're simply not within their power.

Those studies do not have the ability in a scientific sense to rule out these other options or possibilities.

Q Okay. Slide 21 now.

A So another way of putting this example is that chance alone could have easily produced the observed risk ratio of one even if the study were

perfect, even if these were not just epidemiologic studies based on records of all their problems.

It's never the case that these studies are perfect, but even if they were perfect chance alone could have easily produced the observed no association if the true risk ratio were .5 or two.

Q Okay. Next slide?

A Now, another crucial point is that significance tests and confidence intervals ignore nonrandom errors. Hence, confidence intervals should be taken as showing the absolute minimum range of risk ratios compatible with the data.

In other words, they're giving, and this has been stated in the literature, the peer reviewed literature by Paul Meier, who was a renown medical statistician from the 1950s and 1960s. The Kaplan-Meier test is named after him and one of his colleagues.

He said these should be taken as showing the absolute minimum range of values compatible with the data. They're only giving you what would be your uncertainty left if the study were absolutely perfect. They must be widened to account for nonrandom sources of uncertainty.

When you examine them, think of that core

and moving out what blurs it out even further, such as differences in doses in different persons and cohorts as an example of one source of difference among the studies here.

Q That means the confidence intervals, if you think of them in the abstract, would be even wider than the nominal statistical ones?

A That's correct.

Q Now Slide 22. Did you review the epidemiological studies on mercury-containing vaccines in neurodevelopmental disorders that were cited by the defense and then look for any more you could find?

A Yes.

Q What did you conclude from that review of the epidemiological literature on mercury-containing vaccines and neurodevelopmental disorders?

A I didn't find any published or see any published, peer reviewed, controlled epidemiologic study of TCVs and regressive autism per se. All studies that I saw identified -- that is failed to separate -- regressive autism from other types of autism, and certainly none of them looked at clearly regressive autism in a controlled epidemiologic study.

Q Okay. Slide 24?

A Here are the studies that I saw identified,

given some credibility by most of the reviewers, including Dr. Fombonne.

Q That's just the list of them?

A That's just the list.

Q You're going to go through them in a second, I take it?

A Right.

Q Okay. Let's go to the next slide, 25.

A The study by Hviid, reported risk ratio for any TCV. This is any exposure versus none, so it didn't matter if the doses were incomplete and so forth, if there was an incomplete vaccination series.

It reported a .85 with 95 percent confidence limits of .60 and 1.2 and a risk ratio for the highest dose category -- now going to the highest dose category where they receive three doses of mercury-containing vaccine. That was a point estimate of .96, but the 95 percent limits were from .63 to 1.47, so the results from that study would allow for substantial association with clearly regressive autism.

Q In other words, this study by itself is not at all incompatible with a true effect of TCVs on purely regressive autism?

A That's correct.

Q Okay. It doesn't rule it out?

A Not at all.

Q Okay. Slide 26.

A It's important to note that I think the children in the study have roughly half the total mercury exposure in early childhood from the vaccines as in the American vaccination schedules, so the study should be expected to exhibit a weaker association of TCV with autism than would an American study if there were such an association. Its confidence limits should be expanded accordingly.

Q And now Slide 27, the next study?

A The Andrews study from 2004 had 95 percent limits of .88 and 1.12.

Again, the vaccination schedules that I saw reported in this study correspond to roughly half the American schedule, so again it would be expected to exhibit a weaker association with autism than would an American study, and its confidence limits would have to be expanded accordingly to apply to the American children exposed to the schedules.

Q Okay. And then the next slide on this study? These are two more studies?

A Two more studies cited. One, Heron, was another UK study. It reported no analyses for autism

that I saw, and another by Jick and Kaye, again among UK subjects, where the confidence interval was from .7 to 3.3.

Again, these are using studies that are looking at a population that had lower than American doses according to what I read in these reports and others.

Q Now we're going to go to Slide 29, which is about the Verstraeten study done in the U.S.

A Okay. Well, the confidence intervals in this study were wide, ranging from .62 to 1.46 and at the highest category .55 to 3.48.

The conclusion reached by the first author was an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and therefore more study is required. He stated that in a letter to *Pediatrics* following the study.

Q Let me ask you. If the defense experts and the defense lawyers argue that this series of studies we've looked at provide convincing evidence that there's no association between thimerosal-containing vaccines and clearly regressive autism what would you say about that assertion?

A I'd say I'm not convinced. I would say that it doesn't. The epidemiologic evidence as I've

described it here for the dilution reason that I've given -- if I take into account all the uncertainties associated with these studies, both the statistical error, the summary confidence interval that I would get combining these studies and then take into account the dose differences and what's not understood about the dose differences, that I could not possibly rule out the kind of small risk ratio overall that we saw before arising from a relatively large risk ratio for clearly regressive autism, using the figures that Dr. Fombonne gives in this report.

Q Okay. Now, these studies that we looked at were virtually all -- I guess they all were -- ecological studies. None of them were case control studies, right, the ones we've been looking at?

A No, no. These are all controlled epidemiologic studies. One was a case control study. I believe the others were based on cohorts so far. These were controlled epidemiologic studies.

Q These were the controlled studies?

A Yes.

Q Now you have a discussion of the ecologic studies coming up?

A Yes.

Q Okay. Let's go to the next slide, Slide 30.

A Well, then there were other studies that have been cited or I saw cited that we would call ecologic studies in epidemiology. It's important to distinguish these studies from what I call controlled studies in the earlier slides. They're not considered adequate substitutes for controlled studies, and they're especially unable to reliably distinguish small associations from no association.

I'm citing a book chapter by Morgenstern, the chair of the Epidemiology Department at University of Michigan, and also another book chapter that I wrote for a CDC volume in 2004 where we cite extensive literature.

It's been known for many decades that these studies can produce completely misleading results very easily because they don't disaggregate people and identify individually whether a person who got a particular exposure such as a vaccination got the particular outcome being studied, such as autism.

Q There's no connection to individual exposure in these studies?

A By their nature, they lack data connecting the outcomes of the individuals with autism to their exposures, such as vaccination.

Q Okay. Slide 31?

A Here are three major ones that I have seen cited. They did not analyze regressive or clearly regressive autism cases that I saw, and specific association of TCVs with clearly regressive autism, if it existed, would have been completely submerged so I would say these studies really have virtually no evidential value regarding this particular issue on clearly regressive autism.

Q Okay. Let's go to the next slide about Fombonne's study in particular.

A Looking at Fombonne's study in more detail, it analyzed PDD, pervasive developmental disorder, which is a much broader category that subsumes autism, as well as other disorders, so its results are even more diluted than the other ecologic studies.

As the authors note, not all children in the exposed cohorts of the study were exposed to thimerosal, leading to further dilution. This is another problem with the study.

Q Okay. The next slide, still on the same study. Slide 33 now.

A Well, from the data presented there would be about 60 cases of general autism in the study, so only about a dozen cases of regressive autism and perhaps only four clearly regressive.

Now, regardless of whether that's so, I would say regardless of that the article was uninformative about possible association of TCVs with regressive autism, and a reanalysis of the study data would not be capable of detecting such an association if it existed.

Q Just because of the imprecision of the study?

A Of all the problems that we named before: It's ecologic, it's looking at PDDs, and we have a situation in which there would not be enough clearly regressive autism to elevate the risk enough to be detected beyond the statistical noise level.

Q Okay. So taking all of these studies together, what do they mean with respect to the question here as to whether TCVs cause clearly regressive autism?

A Well, because the currently published evidence cannot rule out a very small association of TCVs with autism, and by that I mean something very close to one, like 1.06 or even closer to one as we saw before.

Therefore, that evidence cannot rule out an association of TCVs with clearly regressive autism, even a risk ratio of two, so the question of whether

TCV is associated with clearly regressive autism remains unanswered by the current epidemiologic literature.

Q Let's do a little math here for a second. Suppose the real risk of clearly aggressive autism tied to the full American schedule is in the range of 1.06 to 1.1, something like that, a six to 10 percent increase in risk.

Even if it's not detectible by these types of studies, if 40 million children receive that vaccination schedule throughout the '90s you're still talking about quite a few number of kids, aren't you, that would be affected?

A Yes.

Q It would be essentially six percent of 40 million at risk, wouldn't it?

A Well, no. The six percent refers to the case series. The six percent would be applied over and above the number of autism cases that would be seen, not to the 40 million.

Q Okay.

A But to however many cases that 40 million would be expected to generate.

Q Well, we could do the math, and we're still talking probably hundreds and hundreds of cases that

would not be detectible by these studies?

A I would expect.

Q Okay. Let's go to the next slide, 35.

Now, here I will comment on some aspects of Dr. Fombonne's report. In relying on it and his expertise in his specialty to discuss these issues, I tried to look closely at his citations and go back to the literature he was citing.

I found that some of the citations were unaccompanied by any evaluation of the statistical strength of the study cited. The strength of those studies -- I'll discuss that a bit more -- is related to the confidence intervals that we would get from them if we indeed calculated or could calculate them or the authors had given them to us.

I do that in one case where there was enough data for me to do that. The studies turn out to largely not have enough statistical power or precision to rule out a hypothesis that there is a link between the TCVs and clearly regressive autism.

I also found that some of the arguments given and studies cited have little or no bearing on whether TCVs could cause regressive autism, and I found some citations that do not show what they're cited as showing. Now, this is with all due respect

to Dr. Fombonne.

I think that these problems, he was not aware of them is my reading of the document and I think was doing this quite innocently, but it relates to the very problem I was discussing in the beginning of people failing to realize that it's important to see confidence intervals and put things in context of all sources of uncertainty when looking at studies like this, but now I'd like to give some examples of these problems that I noted.

Q Okay. Slide 36.

A For example, he claims at paragraph 38, and here's a direct quote: Unusual acceleration of head growth was seen with similar frequency in the regressive group as compared to the early onset group. Then he cites a study by Webb and colleagues in 2007.

This finding again illustrates both the presence of objective developmental abnormality before the regression and the similarities between the regressive and nonregressive groups. That's his quote. That's what he says.

I went and looked at the Webb study very closely just to get a sense of how it was showing this, and I saw that it provides poor statistical and epidemiologic evidence and no logical support for the

idea that TCVs do not affect autism risk.

Here is the reasons: On the statistical side, the Webb article had only 28 cases of autism spectrum disorder total and only 11 classified as regressive, far too few to statistically detect all potentially important differences.

If we consider the clearly regressive autism type, which Dr. Fombonne argued was not maybe a third or a fourth of all the regressive types, there would only be two or three clearly regressive cases in this whole study.

Q Okay. Let's go to Slide 38.

A Then another problem is that the prevalence of cases classified as regressive was 39 percent in the article. That's about two to three times the prevalence as cited by experts that I read and articles that I read, including Dr. Fombonne.

That suggests that many or most of the regressive cases in this study were not truly regressive. When that happens, when you have this incorrect classification of cases, that would obscure any real differences between true regressiveness and other cases.

Now, I would note that in the study they base their classification of regressive, as I recall

correctly, on parental report. There was no further follow-up as was done in some of the DOJ investigations is my understanding, so then it's not surprising that they would end up with quite a few more autistics classified as regressive than you would see in a more careful study.

Q Okay. Let's go to Slide 39.

A Then there's the logical issue. This may be the most subtle point, but also perhaps the most important. Even if regressive cases exhibited the same head growth and abnormalities as the other types, would it actually count against the possibility that TCV can cause regression? The answer is no.

The abnormality may mark a susceptibility to autism, a susceptibility that had been triggered early in most cases and later in regressive cases, so as with the PKU example it's possible to have a retardation trigger earlier or later. Somebody with PKU, with that genetic deficiency, if they start consuming phenylalanine they'll develop brain problems and retardation at any number of ages depending on when that exposure occurs.

Q And the next slide, Slide 40?

A Now, the reason why I emphasize this logical problem is because it applies very broadly to the

cited literature. Considering again that paragraph of Dr. Fombonne's report, he states:

An evaluation of 163 autistic children with regression showed that 72 percent were not developing normally before the regression, and he cites a study by Richler, et al. This is where the 72 percent I used in the earlier calculation came from.

He goes on to state: Thus, abnormal development can be documented in children with regressive autism before the regression occurs, even though the parents are unaware of it.

Q Okay. Go to the next slide, 41.

A Well, first that second sentence, the concluding sentence, ignores that the cited study could not document abnormalities in the other 28 percent of 163 regressive cases. Thus, it only serves to document that clearly regressive cases appear to occur. It actually documents too that if we take it at face value that there are a minority of regressive cases who are a minority of all autistic cases.

The study, the 28 percent, it does not even argue against TCVs causing regression in other cases since children showing abnormalities could include a population vulnerable to TCV effects. It's simply not bearing on the issue here.

Q Let's go to the next slide, 42. You're talking now about another study that Dr. Fombonne cites.

A Another study that Dr. Fombonne cites later by Nelson, in paragraph 61 he cites it, and he's talking about assertive biomarkers of prenatal anomalies.

Dr. Fombonne states: In 99 percent of children with autism, levels of at least one of these substances, referring to these biomarkers, which are not overt clinical signs or symptoms. They're something that has to be measured through a test. At least one of these substances exceeded those of all controlled children among the autistics.

Although the results were not specific to autism, they point unequivocally toward prenatal anomalies in children with autism or intellectual impairment.

Q Okay. Go to the next slide, 43.

A Even if this assertion were accepted at face value it would not in any way detract from the possibility or even the plausibility that TCVs can cause clearly regressive autism.

Such effects could arise precisely because certain subclinical anomalies are present, leaving the

child vulnerable to TCV effect. They could even be clinical anomalies, but I just inserted subclinical there because that's what they were discussing were biomarkers.

Q So they could just be biomarkers of susceptibility?

A That's correct. They could be.

Q As opposed to biomarkers of developed autism?

A That's right.

Q Okay. Slide 44.

A But then when I looked more closely at the Nelson article it examined only 69 cases of autism spectrum disorder. That's the broad category. So any failure to find biomarker differences among autism subtypes could be a simple consequence of insufficient numbers of subtypes.

Again, there were no confidence intervals given and no way to evaluate how much uncertainty would be left by these small numbers, but they must be very small. There can't be many clearly regressive autistics in a series of 69 cases of autism spectrum disorder. There would just be a few.

Now, the last example I want to give and the most problematic for me is that other data cited by

Dr. Fombonne do not show what he asserts they show. Again, I'm not saying he's distorting the literature. I think he simply made the mistake of not looking at what I'm about to go over.

Q Okay. Slide 45?

A He says in paragraph 41, and in 121(e) he also cites this study: Testable predictions could be made if TCVs were hypothesized to be such an environmental trigger.

First, the parents of children with regressive autism born in the 1990s were exposed to much smaller doses of thimerosal and vaccines than were their children. Thus, if the above postulate were true, referring to the hypothesis that the TCVs are an environmental trigger, if that postulate were true we would expect to see a lower rate of autism in these older individuals than in relatives of nonregressive autistic children.

But that is not the case, so he asserts that there is the same rate of autism in these older individuals as in relatives of nonregressive autistic children, and he cites a study which is extensively cited elsewhere by Lainhart, et al. in 2002.

Q Okay. And the next slide, 36? Go ahead.

A I went and examined that study carefully

since it seems to be pivotal to his argument. It turned out that it compared only 18 parents of cases labeled as regressive to 70 parents of cases labeled as nonregressive.

Now, based on the figures that he was giving I would expect, first of all, that among the cases of these 18 parents labeled as parents of regressive there would only again be perhaps what, four or five that would be parents of clearly regressive cases, so these are very small numbers. Also, they compared rates of broader autism phenotype, not autism, as Dr. Fombonne states.

Furthermore, five of the 18 parents of the regressive and 23 of the 70 parents of the nonregressive had autism phenotype according to this study. Thus, the parents of regressive cases did in fact exhibit a slightly lower rate than parents of nonregressive cases.

Q Is that the opposite of what he said?

A Well, it's not the opposite. The opposite would be if they had more, but he said there was no difference, and in fact it was slightly lower going in the direction of what he was saying it wasn't doing.

Q Okay. All right. Next slide?

A Well, I don't want to capitalize on that

oversight because the Lainhart data are too scanty to draw any reliable conclusion.

From there what they published, their numbers, I was able to calculate a 95 percent confidence limit for the difference using methods that are in many textbooks, including our own. The limits that I got were very broad, minus 30 percent to about plus 20 percent.

Regardless, there are other ways of calculating these limits and they could come out differently, but not so much different that it would change this conclusion. The data are quite compatible with the possibility that parents of regressive cases had much lower rates of autism phenotype than parents of other autistics, so the actual data do not show what Dr. Fombonne cited them as showing, which is no difference.

Q Okay. Slide 48. Now you're going to give some responses to Dr. Goodman's report, another of the defense epidemiology experts.

A Correct. Now, this report was very problematic for me because I think that it was very distorted. Unlike Dr. Fombonne's report, it was saying many things which I would question whether Dr. Goodman could get up and defend in a scientific

meeting before an audience of his peers, including myself among them.

It presents absence of evidence as if it were evidence of absence. It exaggerates the information content of the available evidence, and it insinuates that any view departing from his own preferred conclusion are unscientific. This should be his own preferred conclusion.

He makes these arguments based on specious analogies with astrology and unsupported claims about mechanisms, claims that have no supporting evidence at all.

Q You go into some more detail in the next slides on this points, right?

A Yes.

Q Slide 49. Let's go to 49. There we go.

A Here's an example of the kind of exaggerated claims made in his report. He says: The totality of current epidemiologic evidence strongly supports the conclusion that thimerosal-containing vaccines are not related to the development of autistic disorder.

Q Okay. Next slide?

A Let's look at that. Nowhere in his report does he define what it means for epidemiologic evidence to strongly support a conclusion of no

effect.

There's a good reason that he doesn't. There's no agreement among scientists about what kind of evidence is required for strong support or what strong support means, especially for a null hypothesis and a null association of the sort we're debating here and especially in epidemiology.

I hold that epidemiologic evidence can only rarely inarguably, strongly provide strong support -- again, there are words dropped here -- to claims of no effect, and the TCV/autism controversy is not one of those rare instances. I've stated that before, and I'll state it again in counter to what he's claiming.

Q All right. Let's go to the next slide, 51.

A Nowhere does Professor Goodman account for the potential problems of the studies he cites. He does a lot of hand waving citing Bradford Hill and saying how these studies couldn't have major problems, but he doesn't even discuss the major problem of these studies in trying to make an inference about the cases that we're discussing.

Instead, he presents results of the studies in a table and argues that their statistics should be taken at face value and combined. He presents no estimate of the uncertainty that would be warranted if

methodologic issues such as the difference in dose levels between the different countries in which these studies were conducted, if those were allowed for.

Q He doesn't even talk about dose differences?

A I didn't see where he made any accounting for it. He made mention in passing.

Q Okay. Slide 52?

A He presents no further analysis to show that these studies rule out subtype effects. None of the data he presents concerns subtypes, so he doesn't even go through the kind of calculations that I was discussing earlier.

Instead, he claims that the combination of studies which show high precision, as does Dr. Fombonne in his paragraph 121(f), both fail to recognize that the dose differences among the studies would lead to wider confidence limits than they expect, wide enough to allow for an overall risk ratio of six percent, which I want to remind us that that's the upper bound that Fombonne put on the increase from clearly regressive cases if there was a doubling of risk of those.

Q Okay. The next slide is more about Dr. Goodman's report.

A He further argues that the regressive

subtype is scientifically unfounded, a scientifically unfounded category akin to astrologic sign, in flat contradiction to numerous experts and studies, including Dr. Fombonne at paragraph 83 where he recognizes that subtype and the Richler study which provides evidence that it's real.

They recognize the subtype as a legitimate clinical entity by virtue of having cases that have no earlier symptoms that they could detect. I think his arguments here are nothing more than rhetorical nonsense.

Q Slide 54 shows some of those.

A Astrologic sign has no resemblance to TCV. TCV involves direct injection into the body. In contrast, astrologic sign refers to stars light years away.

The fact that TCV is injected, that fact has fueled concerns about its impact whereas it's the enormous distance of the stars and the planets that make astrology seem so outlandish. If astrology was replaced by something talking about an exposure in the house like fumes emitted from carpets it wouldn't be an outlandish topic.

He cites this Peto study that's famous, but that study isn't about what's going on here. It

concerns artifacts arising from analysis of multiple subgroups, many subgroups in clinical trials. Here are 12 astrologic signs, and we know that by chance when you examine a lot of subgroups you're bound to find some things that are statistically significant, even if there's nothing going on.

But the point at issue for me today and here and in the literature that I have been citing is about a single subgroup within a subgroup that's been talked about at length in the literature, regressive autism, and then that smaller subset which hasn't been talked about in as much length, but appears to exist from the Richler study and even seems to be conceded by Dr. Fombonne.

Q Okay. And by the small group, the small subgroup within the small group, you're talking about the truly regressive autism?

A Yes.

Q Yes. Okay. All right. Let's go to the next slide, Slide 55.

A So to go on about how ridiculous it is and to call into question his credibility here, and I mean to intentionally. There's not even a speculative mechanism as to how the stars or planets could influence individual health.

Whereas mechanisms have been proposed whereby which thimerosal could affect regressive autism. For example, in Kinsbourne's report on general causation. Now, I am not saying that those mechanisms are real. I am not saying that they are generally accepted. I am not saying anything of that sort. I'm simply pointing out that people who have worked in this area have presented these mechanisms.

They have been criticized. I'm well aware of that. I am not an expert in that area. I'm not here to comment on that. It's simply the fact that there is nothing approaching that regarding astrology, and that analogy he's drawing as far as I'm concerned is something that would belong in a bad political campaign, not in science.

Q Okay. Let's go to the next slide, Slide 56.

A Then he goes on and invokes fictional -- they're completely fictional scientific principles claiming that arguments are scientific only if that patient is distinguishable from a larger subgroup on the basis of a recognized causal or mechanistic factor.

This distinction based on disease phenotype, e.g. regressive autism, are only meaningful if that phenotype is shown to be associated with a different

causal pathway or has a fundamentally different biology than other phenotypes.

Q Okay.

A That's on page 9 of Professor Goodman's report.

Q And you say that what he's arguing there is not scientific at all?

A Not at all.

Q Slide 57? Go on.

A All he's asserting here is that in the absence of evidence we should dismiss anything that fails to conform to this prejudice regarding mechanisms.

In particular, he's claiming that we should assume the same mechanism is operative among distinct disease types whenever we don't know the mechanisms that cause a disease. If you go back to the previous slide to take his quote directly if you can --

Q Let's go back.

A I'd like to make this point.

Q Let's go back to Slide 56.

A He says: Distinctions based on disease phenotype are only meaningful if that phenotype is shown associated with a different causal pathway.

He's stating as a general principle. Where

was this principle when people started to distinguish leukemia subtypes? Dr. Goodman is an oncologist, among other things, so he should well know that people were distinguishing subtypes of leukemia based on observable differences before anybody had any good idea on the sources and causes of leukemia.

Even today, all the causes of leukemia are not well mapped out. Most of the cases do not have an identified risk factor, even though there are some causes that are known like intense ionizing radiation. People throughout medicine distinguish phenotype and even recognize that the mechanisms could be different, in fact may well be different, based strictly on observed differences, different types.

Gradually, as medical science progresses, for example, people started to recognize that there were different subtypes of lung cancer. That was before people finally realized that there was one particular subtype that was dramatically increased by smoking where you're talking about a relative risk of 10 or 20. It wasn't even an accepted association until the 1960s or 1950s at the earliest. Doctors were still promoting cigarettes as health aids clear up to 1950.

Q Okay. Let's go to the next slide. I guess

58 is what we want to go to now.

A Well, actually we didn't --

Q What slide would you like?

A Well, we'll go on to the next one.

Q Okay. Slide 58.

A So to see why Dr. Goodman's claim has no scientific substance, it's important to understand that the causes of autism in general, let alone the regressive type, are not understood in any way that has been demonstrated empirically, nor are the mechanisms.

As a profound demonstration of the ignorance of autism experts, these experts have failed to conclusively identify the causes of the rise in reported autism incidence and have failed to predict its continuing course.

Now, I'm not saying that the rise in autism incidence is real or part of a diagnostic issue. Dr. Fombonne seems to be convinced that it's largely diagnostic. It may well be, but at this point there seems to be disagreement remaining in the literature regardless of what people say about TCVs about what are all the factors responsible for this increasing report of incidence of autism. Nobody has been able to predict how its course is going to go successfully.

Q Okay. Let's go to Slide 59.

A Dr. Goodman claims that absent any evidence one way or another we should simply assume that early autism and regressive autism are caused by identical mechanisms. This is the strong assertion in need of proof.

He has basically shifted the burden of proof away from a strong assertion that they are the same mechanism and towards an admission that perhaps they're not the same mechanism or perhaps there are some mechanisms they share and others that they don't.

Dr. Goodman offered no evidence that the mechanisms behind the two types are identical because there is no such evidence. This argument is just coming from his authority. It's not scientific. I don't take that because I'm Dr. Greenland. I'm Dr. Greenland. You should take my word for it. You should look at the evidence. He doesn't give any. As far as I can see, there isn't any.

Q Okay. Let's go on to the next slide.

A So as I said, he attempts to shift the burden of proof to those who would allow -- simply allow -- that different disease types could involve mechanistic differences. I think his claims are nonsense in both scientific and every day terms.

It is open minded and hence scientific to allow for the full range of possibilities, including differences in effects, in the face of such extensive ignorance about the mechanisms of autism development. It's unscientific to assert that there is no difference in mechanism when there is no understanding of mechanism or very little.

Q All right. I think that summarizes your testimony. We have a couple slides again just to make your main points again. If you would reiterate those, please?

A So again the epidemiologic literature has not ruled out the possibility that thimerosal-containing vaccines are associated with a prespecified type of autism of the regressive form, and that's been my point.

Not to say that there is such an association, but simply that the evidence that I am a qualified expert to discuss doesn't rule out that possibility.

Q Okay.

A And specifically upon which controlled studies have not analyzed clearly regressive autism. Clearly regressive autism is very uncommon, so there are very small numbers of cases in the studies to

date.

Hence, even if the studies have separated the clearly regressive cases or even if we got their data and could separate them out, a true association could easily be missed -- could have been missed and could easily be missed -- because the numbers aren't there at this point.

MR. WILLIAMS: Okay. Thank you very much. That's all the questions I have.

SPECIAL MASTER HASTINGS: All right. Let me ask. It is now 12:30. Do you want to go ahead and start with your cross-examination of Dr. Greenland?

MR. MATANOSKI: No. We'd rather break for lunch if we may.

SPECIAL MASTER HASTINGS: Okay. Had you talked with the Petitioners about the issue of the break for lunch?

MR. MATANOSKI: Yes. Yes, we did, and we both acknowledge that we could shorten it a bit. We thought maybe 45 minutes.

SPECIAL MASTER HASTINGS: Forty-five minutes?

MR. POWERS: Forty-five minutes, which puts it about 1:15.

SPECIAL MASTER HASTINGS: 1:15. All right.

MR. MATANOSKI: If I may?

SPECIAL MASTER HASTINGS: Go ahead.

MR. MATANOSKI: Could I ask for a copy of the 62 pages of slides --

SPECIAL MASTER HASTINGS: Yes. I wanted to discuss that.

MR. MATANOSKI: -- for the lunch break so that we could take a look at those?

SPECIAL MASTER HASTINGS: Right. Just for those folks who are at home, we are going to take a 45 minute lunch break and start again at 1:15. We're off the record at this time.

(Whereupon, at 12:30 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 1:15 p.m. this same day, Monday, May 12, 2008.)

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

(1:20 p.m.)

SPECIAL MASTER HASTINGS: Good afternoon, folks. Please be seated.

For those of you who are at home, we are about to begin the afternoon portion of the proceedings today. We have Dr. Greenland back in the witness chair, and the Respondent was going to begin cross-examination of Dr. Greenland.

Go ahead when you're ready.

MS. RICCIARDELLA: Thank you

SPECIAL MASTER HASTINGS: It will be Ms. Ricciardella here.

Whereupon,

SANDER GREENLAND

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

CROSS-EXAMINATION

BY MS. RICCIARDELLA:

Q Good afternoon, Dr. Greenland.

A Good afternoon.

Q Now, your expert report in this litigation is written very carefully. You were very precise in the way in which you stated your position, and I want

to be clear for myself and for the Court what you were saying and what you weren't saying in your report.

Now, my understanding of what you're saying is that even though the body of epidemiologic literature has found no association between thimerosal-containing vaccines and autism spectrum disorders, it's still theoretically possible that such an association exists with a small subgroup, namely those who develop regressive autism, correct?

A I would change one word order there, and that's --

Q Go ahead.

A -- the epidemiologic data has not found an association, but the rest I would say yes.

Q But it's theoretically possible that it still exists in a small subgroup, regressive autism? What I'm actually understanding you to say today is clearly regressive autism. Is that correct?

A Correct.

Q And you did a variety of calculations in your report to show theoretically how high that risk could be, correct?

A Correct.

Q Now, you did state in your report on page 16 that the brief overview given above, meaning of the

epidemiologic studies that had been done to date, supports the idea that the association of you say MCV. I say TCV. When you say TCV you know what I'm talking about?

A Yes.

Q It's a mouthful to say thimerosal-containing vaccines, so I'll use the acronym. The association of TCV with autism is small or nonexistent. Do you recall writing that in your report?

A Yes.

Q Do you still agree with that?

A Yes.

Q Now, there have been a few studies that have purported to find an association between thimerosal-containing vaccines and autism, and you refer to those in your report as ostensibly positive studies. I'm referring to those done by Dr. Mark Geier and his son, David.

A Yes.

Q Have you reviewed those studies?

A I have read them.

Q Okay. And you noted though that those studies have been criticized by other reviewers, correct?

A Correct.

Q Have you formed your own assessment of those studies?

A I concurred with the reviewers. This is why I did not include them in my review.

Q You found those studies to be not credible?

A I would put it as deficient in methodology such that I would not count them as evidence if others were willing to go along with that.

Q Now, Doctor, if there was indeed an increasing incidence in the overall number of autism cases that some have termed an autism epidemic and if it was shown that thimerosal-containing vaccines were the reason for that increasing incidence, would that increase likely be picked up by the epidemiologic studies?

A If it was restricted to a subgroup then it wouldn't have.

Q No. I'm not talking about subgroups. I'm just talking about there's been a purported autism epidemic. If there's really indeed an increasing incidence in the number of autism cases that some have termed an autism epidemic, would that be detected epidemiologically?

A I think I'm not understanding your question. Please restate it.

Q If there was an increasing incidence in autism, if the number of cases of autism were increasing tenfold, for instance, and if that increase were due to thimerosal-containing vaccines, would that be picked up by epidemiologic studies?

A Yes, a tenfold increase certainly would be.

Q And would you agree that the body of epidemiological literature has not supported the hypothesis of an autism epidemic?

A My understanding is that there is an increasing diagnosis of autism. The cause of that, whether it's diagnostic changes or actual changes in the occurrence of the disease, seems to be a matter of convention from my understanding.

Q I'm asking hypothetically. If indeed it was shown that there is an autism epidemic, would you agree that the epidemiological literature does not support the hypothesis that an epidemic is caused by thimerosal-containing vaccines?

A I would agree.

Q I want to be clear about your opinion in this case or in this litigation. Is your opinion predicated on the assumption that children with clearly regressive autism have an elevated risk due to thimerosal, and children with nonregressive autism

have little to no elevated risk due to thimerosal?

A Which portion of my opinion? Some parts make the assumption for the calculations that I made that the risk was only increased by thimerosal for those with clearly regressive, but other parts of my argument didn't refer to that assumption.

Q In the slide presentation that you presented during your direct testimony, some slides referred to regressive autism as being the subgroup under consideration, and some slides referred to clearly regressive autism.

Which one are you saying is purportedly associated or that the epi studies have been unable to detect?

A Well, the general argument is that if there is a subgroup that is as uncommon as, for example, clearly regressive autism would appear to be then whatever that subgroup may be the epidemiologic studies could not have picked up an increase in risk in that group if it had been confined to that group, even if it was a large increase.

Q So if the risk is confined to that group the clearly regressive autism, are you assuming then that there is no elevated risk to any other group, any other cases of autism?

A In the calculations I made, yes.

Q Now, Doctor, you don't claim in your report and I don't understand you to be claiming here today that you have any expertise in autism, do you?

A I am not claiming that.

Q And you are not claiming in your report or here today that you have any expertise in regressive autism in particular, correct?

A I am not claiming that.

Q How do you define regressive autism?

A Simply by whatever definition is being used in a report. I go along with it, not being an expert in the --

Q What report?

A It depends on which study we're talking about. For example, one of the reports -- I forget the primary author -- described regressive autistic cases among their case series. Well, several did.

For the purpose of analyzing that report, I would then simply accept whatever the authors were using, as well as Dr. Fombonne when he would discuss the matter as well.

Q Now, on page 1 of your report you call regressive autism a prespecified type of autism. Why did you use the term prespecified?

A That was with respect to the idea that it might have been defined after the fact solely based on exposure to thimerosal.

Q After what fact?

A After the introduction rather of the hypothesis that TCVs cause autism.

Q Who told you about that hypothesis?

A I don't remember when I first read of it. I remember seeing things in the news long ago, but I don't recollect exactly.

Q And who told you that? Where did you hear that thimerosal-containing vaccines cause regressive autism only?

A I don't recall where I first saw that.

Q Now, Doctor, did you present in your report any evidence that regressive autism is a form of autism that is biologically distinct from any other cases of autism?

A I did not.

Q And can you present any evidence that would lead you to distinguish regressive autism biologically from nonregressive cases of autism?

A I would have to rely entirely on other experts.

Q And you didn't present in your report any

evidence that the causal risk factors for regressive autism are different than the risk factors for other cases of autism, correct?

A That's correct.

Q Can you tell us what the risk factors for autism are in general?

A I know that there is supposed to be some syndromes, genetic syndromes that are associated with it, but that most of the cases, from what I'm read, are supposed to be sporadic, of unknown origin.

Q And can you offer evidence that shows that thimerosal is a risk factor for autism, regressive autism, but not for other cases of autism?

A I cannot.

Q Are you aware of any published literature stating that regressive autism is caused by thimerosal-containing vaccines?

A Could you repeat that, please?

Q Certainly. Are you aware of any published literature that states that regressive autism is caused by thimerosal-containing vaccines?

A Well, I'm aware of published literature that states that.

Q Where? Which literature?

A Well, it appears to me that the Geiers, for

example, make this type of claim, so if you say just published literature --

Q Besides the Geiers, are you aware of any other literature that makes that claim?

A Well, I've certainly read other items, writings -- not necessarily peer reviewed or scientific -- that made these claims.

Q But you can't recall today what those are?

A No.

Q Are you aware of any study that has suggested the hypothesis?

A No. Excuse me. No. Let me correct that. I'm certainly aware of the Geier study and so forth.

Q The Geiers' epidemiological studies that you agreed had methodological problems?

A That's correct.

Q Doctor, if I understand your opinion in this litigation, you're not stating an opinion as to the likelihood that such a regressive subgroup exists that's uniquely susceptible to thimerosal-containing vaccines, are you?

A That's correct. I'm not.

Q And you're not claiming here that it's been scientifically shown that the subgroup exists, are you?

A That's correct.

Q So your opinion is not that the subgroup actually exists. You're saying that it's theoretical possible that it exists, correct?

A Well, no. There is some evidence and support in, for example, the study cited by Fombonne, by Richler, which apparently looked for background factors in the regressive autistic cases.

Q Did they talk about thimerosal?

A No.

Q I'm talking about the subgroup of regressive autism that's uniquely susceptible or I should say clearly regressive autism because that's what you're focusing on today.

A Yes.

Q The subgroup of clearly regressive autism that's uniquely susceptible to thimerosal-containing vaccines. You're not saying that it actually exists?

A I misunderstood your compound.

Q No problem.

A What I was stating there was that it appears from the literature there is a clearly regressive subgroup, and on the other hand I am not aware of any literature that supports the idea that there is a clearly regressive subgroup specially susceptible to

thimerosal, but my comment was simply that that hasn't been investigated so there isn't evidence bearing on it.

Q Okay. But you're saying that if such a subgroup does exist it's rare enough that it has gone undetected by the epidemiologic studies, correct?

A That's the way it looks to me.

Q Doctor, theoretical possibilities though are applicable to any study, aren't they?

A Certainly.

Q I mean, we could refute known associations or lack of associations just based on hypothetical subgrouping of the study subjects, can't we?

A Well, perhaps I could give an example since I'm not 100 percent clear on what you're asking, but to take an example that would I think make it obvious with smoking and lung cancer.

This is an association which is enormous, and people noticed associations of smoking with lung disease as far back as the 1600s when tobacco began spreading in Europe, but it took all the way into the 1960s before the Surgeon General went so far as to recognize it as a health hazard and published a report on that.

Nonetheless, to this date we also know and I

think fewer people realize that most smokers don't get lung cancer, and we don't know why. We don't know what it is about particular individuals in every detail, in every case at least, that leads to them getting lung cancer when they do smoke.

So even though it's something that is very well known, there is still to this day and after a half century of intensive research much unknown, which would be an issue, for example, if this was one of the cases in which people were suing tobacco companies because of their disease. In fact, it's arisen.

So there always remains even in a case as extreme as that where there's centuries of observation and a half century of intense scientific research and well-recognized causation. Even in a case like that, to this day there are points of contention. That's how science is in reality. It's supposed to affirm for all time 100 percent knowledge with medical science.

Q Right. I think you're saying what I was suggesting. To take your example of smoking and lung cancer, I could say yes, studies have shown an association between smoking and lung cancer, but I can say to you well, Doctor, how do you know nobody has ever looked at whether smoking causes lung cancer in

tall men with brown hair.

Or I could define the subgroup to say no one has ever looked at the association between smoking and tall men not just with brown hair, but with dark brown hair. You could take it on and on, correct?

A Well, what I would expect more to hear, and in fact this is something that people talk about, is what is it about the vast majority of smokers who smoke heavily through their life and don't get lung cancer?

The search is there for the genes that would identify those who do and those who don't get lung cancer, so indeed there's a focusing on subtypes, but not brown hair. I haven't heard that used as a risk factor of autism.

Q Well, because it's a ridiculous example, and it's ridiculous because I haven't offered you any explanation as to why tall men with brown hair are somehow different than the populations that have been studied, correct?

A Correct, but there are factors where there are theoretical explanations, and people continue to pursue these issues.

Q Now, Doctor, I understand your opinion is that the epidemiologic studies don't disprove the

hypothesis that thimerosal-containing vaccines cause clearly regressive autism, correct?

A Correct.

Q But you're not saying, are you, in this litigation that the studies proved the hypothesis either, are you?

A Correct. Definitely not.

Q And in your report you don't actually state the likelihood of an association between thimerosal-containing vaccines and clearly regressive autism, do you?

A No.

Q Doctor, is there any evidence that clearly regressive autism is more likely than not caused by thimerosal-containing vaccines?

A I'd say all the evidence that I've seen discussed has some bearing on it, so --

Q I didn't ask about bearing. I asked is there any evidence that it's more likely than not that thimerosal-containing vaccines cause clearly regressive autism?

A You said any evidence. My specialty is epidemiologic evidence, so if you would narrow it to that?

Q Well, how about epidemiologic evidence?

A Epidemiologic evidence? Then I would agree with your statement.

Q Doctor, as a member of the scientific community do you believe that clearly regressive autism is caused by thimerosal-containing vaccines?

A I don't have any belief one way or the other.

Q Do you have any belief one way or the other that autism is caused by thimerosal-containing vaccines?

A I do.

Q Okay. What's your belief?

A Well, let me --

Q I'm talking about autism in general.

A Autism in general. That if there is an effect, I would bet that if there is an effect it must be concentrated if there is. Notice the hypothetical, please. It must be concentrated in a very small group to have gone undetected to this point in time.

Q But you can offer no evidence that such a group exists, correct?

A That's correct.

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

SPECIAL MASTER HASTINGS: Any redirect?

MR. WILLIAMS: I have no redirect.

SPECIAL MASTER HASTINGS: No redirect?

MR. WILLIAMS: No redirect.

SPECIAL MASTER HASTINGS: Okay. All right. Dr. Greenland, thank you very much. You're excused at this point.

THE WITNESS: Thank you.

(Witness excused.)

SPECIAL MASTER HASTINGS: Should we proceed with Dr. Aposhian at this point?

MR. WILLIAMS: We have some logistics to get him to the airport. Can we have five or 10 minutes right now and then start Dr. Aposhian?

SPECIAL MASTER HASTINGS: All right. Let's take a brief break. We'll start back with Dr. Aposhian as soon as you're ready.

MR. WILLIAMS: Thank you.

SPECIAL MASTER HASTINGS: Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: We are ready to go back on the record. We are going to proceed then with Mr. Williams' examination of Dr. Aposhian.

Dr. Aposhian, would you raise your right hand?

//

Whereupon,

VASKEN APOSHIAN

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

SPECIAL MASTER HASTINGS: Please go ahead, Mr. Williams.

DIRECT EXAMINATION

BY MR. WILLIAMS:

Q Dr. Aposhian, I know that you have testified before the Special Masters before, but for this record I do want to briefly run through your qualifications again. Would you tell us what is your current status in academia?

A I am Professor Emeritus of Molecular and Cellular Biology, my primary appointment, and also Professor Emeritus of Pharmacology in the School of Medicine at the University of Arizona.

Q And are you still active in the scientific arena?

A Yes. I have grants from foundations and grants from the federal government to do research, and my lab is still going.

Q Let's go to Slide 3, please.

A I have no slides up here.

MR. WILLIAMS: You don't see the pictures?

His monitor is not on.

SPECIAL MASTER HASTINGS: Just for the record, let's mark the paper copy of his slide presentation as Petitioners' Trial Exhibit 2.

(The document referred to was marked for identification as Petitioners' Exhibit No. 2 and was received in evidence.)

BY MR. WILLIAMS:

Q Can we try to go forward with you reading this, or is that not going to work?

A Whatever you wish.

MR. WILLIAMS: I hate to waste more time, but he can't see his --

SPECIAL MASTER HASTINGS: We've got a technical expert here. Let's go off the record.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: We're back on the record.

Mr. Williams, resume your examination.

SPECIAL MASTER HASTINGS: Thank you.

BY MR. WILLIAMS:

Q Dr. Aposhian, what is your education?

A I have a Bachelor of Science degree in

Chemistry from Brown University, a Master of Science and a Ph.D. in Physiological Chemistry from the University of Rochester.

Q And then did you spend time at Stanford University after you got your Ph.D.?

A Not exactly. I had an academic position at Vanderbilt University, and I resigned that tenure track position to have the opportunity to work with a man who a year later got the Nobel Prize -- it was very valuable to me -- to learn biochemical genetics, enzymology and basic biochemistry from Arthur Kornberg, one of our best biochemists.

Q Now turning to Slide 4, have you published a number of articles in the peer reviewed literature?

A Yes. I don't keep track. I would say over 200, but in my CV I don't put numbers. I've also been the associate editor of a number of journals and have peer reviewed many, many papers for various journals.

Q And is your work still cited frequently in textbooks and other scientific literature?

A Yes, and we were very pleased to hear from the editor of *Chemical Research and Toxicology*, which is sponsored by the American Chemical Society, that in the year 2006 the most downloaded article for this journal was an article by me and my wife.

Q And has a lot of your published work dealt with heavy metal toxicology?

A Yes, almost completely.

Q All right. Now, did you prepare an outline of what you're going to talk about today?

A Yes. Would you like me to go over it?

Q I think it would be helpful very quickly, yes.

A All right.

SPECIAL MASTER HASTINGS: That's on Slide 5, is it not?

MR. WILLIAMS: Yes, Slide 5. There's Introduction. I want to begin with an introduction in which I'll define evidence-based toxicology. No. 2, Basic comments regarding modern toxicology; introductory remarks regarding autism spectrum disorders;

A brief review of mercury toxicology; methyl mercury, thimerosal and ethyl mercury; brain concentrations of mercury species; developmental biology and autism; and the first hypothesis: One cause of autism is cells cannot efflux mercury, including thimerosal ethyl mercury.

The second hypothesis: Terbutaline is an example of a teratogen that can cause some types of

autism via a neuroinflammation mechanism. Under this we'll discuss Terbutaline. We were going to discuss teratogens. I think we may have taken that out. I'm not sure. No. 9, Thimerosal and ethyl mercury. Pink disease we took out. We didn't have a chance to change that. And then I'll present a summary.

BY MR. WILLIAMS:

Q Okay. Now, on Slide 6 there are a number of definitions of measures. I don't want to take the time to go through this now, but we prepared this for reference purposes later if we need to come back and figure out how to convert one measure of a concentration to another. Is that right?

A Yes. Yes.

Q Okay. Let's leave that be for now. We may need to come back to it.

All right. Slide 7. You prepared this. Would you go ahead and explain why you wanted to --

A Yes. I wanted to make some comments that I think are relevant.

First of all, science by definition is a search for the truth. Autistic children are not normal. What is or are the abnormality or abnormalities at the molecular level of autistic children we do not know.

What do first class scientific investigators do when they don't know? They formulate a hypothesis. That is the purpose of my testimony; to formulate a probable hypothesis that thimerosal is involved in some manner, either directly or indirectly, either prenatally or postnatally in the etiology of autism specifically affecting the brain.

Q Okay. Now, you used the term earlier evidence-based toxicology. What is evidence-based toxicology? This is on Slide 8.

A Most of my testimony and slides are not my expert opinion. I want to make it very clear. What I'm presenting are the data, the evidence or comments from peer reviewed papers or from symposium that have usually been peer reviewed.

Throughout this testimony, these peer reviewed comments are in dark blue font. My personal expert opinion when I do occasionally put it forth is in red font. As many slides as possible are labeled or include a literature reference, so again it's not my opinion on those slides.

Most of my testimony and slides therefore deal with a relatively new term; that is, evidence-based toxicology. I'm presenting you what other experts have written in peer reviewed articles.

Q Now, you also have some comments you want to make about modern toxicology.

A Yes. May I have the next slide, please? The next slide, please?

Q This is Slide 10.

A Slide 10. Now, let me say at this point that many people don't understand that people in science have disagreements, and even though the disagreements are based on how they interpret something differently there is no disrespect intended and so under no circumstances --

For example, I've known Tom Clarkson for years, and I have a tremendous respect for him. Obviously I have different opinions, as he does, on certain factors that will be presented, but I want to make it clear that these are differences in interpretations, not meant to be personal in any way.

So let's say does dose determine the poison? We now know in 2008 other factors also determine the poison, and now I'm quoting from the classic textbook in toxicology from a chapter written by Robert Goyer, a toxicologically oriented pathologist, and Tom Clarkson, who is one of the Respondent's, and in this chapter, which is chapter 23, I've taken Table 3-1 out verbatim.

It points out: Factors influencing toxicity of metals; interactions with essential metals; formation of metal protein complexes; age and stage of development; lifestyle factors; chemical forms aspeciation; immune status of the host. These are factors that influence the toxicity of the metal.

As the next slide will point out, this is a chapter again in the same textbook, a different year I think, by Melinsky and Klaassen. Klaassen is one of the most eminent toxicologists we have in this country. He's probably on more national committees, more government advisory committees, than anyone else that I know in toxicology.

I quote now: As we described earlier, the most critical factor influencing toxicity is not necessarily the dose, but rather the concentration of a xenobiotic at the site of action, a xenobiotic being a foreign chemical by definition. Xenobiotics are delivered to most organs by the systemic circulation. Therefore, the fraction of a chemical that reaches the systemic circulation is of critical importance in determining toxicity.

Several factors can greatly alter the systemic availability, including 1) Limited absorption after oral dosing; 2) Intestinal first pass effect; 3)

Hepatic first pass effect; and 4) Mode of formulation, which affects, for example, the dissolution rate, how the stuff comes to part or goes into solution, or incorporation into the micelles for lipid-soluble compounds.

All substances are poisons. This is a direct quote. There is none which is not a poison. The right dose differentiates poison. That's by Paracelsus, who lived between 1493 and 1541.

Toxicology has progressed since then. It's almost 500 years, all right, so again dose is not the only factor that determines the poison and we'll come back to this over and over again during this presentation.

Q Okay. Let's go to the next slide, Slide 12, please.

A This is on the web, the IOM, the Institute of Medicine Forum on Autism -- not on vaccines, but on autism -- and the Environment, which was held in April 2007. This is a quote from Phillip Landrigan, who is a professor of pediatrics and also an epidemiologist at Mt. Sinai School of Medicine, one of the best we have:

Chemicals in the environment can injure the human brain. Children are especially vulnerable to

brain injury caused by chemicals, and this vulnerability is generally greatest during the nine months of pregnancy and the earliest years of life. The brain injury caused in children by chemicals is sometimes symptomatic, but more often produces a range of abnormalities that impair function and that can be detected only through special testing.

The next slide, please? Children are not little adults. We try teaching our students that over and over again. Children are not little adults. As shown below, it takes a premature neonate on the average almost four times longer to get rid of a chemical.

What is plotted here on the left is children's half-time relative to adults, half-time being how long it takes to get rid of half of the concentration. On the bottom we're plotting the various stages. As you can see, especially when you look at the first bar graph, that's almost four times greater than what would be called normal at the number one level.

Next slide, please?

Q Let me just ask you on this one, though.

A Yes?

Q The third bar over is the bar for children

who are one week to two months of age.

A Yes.

Q Is that still statistically significant above an adult's ability?

A Yes, it is. It is. If you go back to the original paper you'll see it is. That's the third one. Yes.

Q Okay. All right. Now, you have some remarks prepared about autism spectrum disorder, going to Slide 15.

A Yes. Now, if you remember from your college chemistry or college physics, a spectrum consists of well-defined bands.

Next slide, please? And this is the visible spectrum that you see with very definite colors from one end to the other.

The next slide, please? Now, as far as autism spectrum disorders are concerned, there are no bands, and most clinicians will admit this; that we have Asperger's, the high functioning ASD kids, at one end and severe autism, the very barely functioning children, at the other end, but in between there is not very much.

This has caused Dr. Spence, who is at the National Institutes of Health, to say we need a

standardized definition of autism and related disorders. This is one of the major problems in trying to define these different kinds of autism spectrum disorder.

Next slide, please?

Q This is Slide 17.

A Autism is a complex disorder. Autism is a multi-system disorder whose outcome is likely to be more profoundly impacted by the environment than any other disorders and diseases. This is put forth by a professor at the University of California-Davis again at this superb IOM autism workshop that was held last year.

Three percent of all developmental defects are attributed to exposure to toxic chemicals. Twenty-five percent of all developmental defects may be due to a combination of genetic and environmental factors.

Next slide, please?

Q Slide 18.

A Now, I introduced this slide because I think it says a number of things. This again was presented at the Institute of Medicine workshop. Again, it's on the web as a recording of that workshop.

Autism is estimated to cost $3.2 million per

child over a lifetime. Using the conservative estimate in the United States of 500 children means the epidemic will cost society close to $2 trillion. $2 trillion. Many families are on the brink of bankruptcy as they struggle to get insurance and the medical attention their children need.

Recently clinical investigations have identified numerous co-morbid disease states in children with autism. These include other disorders that go along very often with autism:

Immune system abnormalities; inflammatory bowel disease; oxidative stress; disordered urine and serum chemistries; including elevated porphyrins; methylation disturbances; increased body burden of metals, including mercury and lead; chronic viral, fungal and bacterial infections; and also, as I put in and added to this, microglial activation in the brain, which we'll also speak about in a few minutes.

Q Okay Can you tell us what you mean by oxidative stress?

A Because of a number of physiological challenges or exposures, the body begins to make free radicals. These free radicals are very reactive chemical substances, and they can damage the structure of DNA, they can damage the structure of proteins, and

they can damage other structures, so it's a very critical kind of injury that one likes to prevent, and one can prevent that by giving antioxidative stress protection.

Q Are there recommended diets and recommended therapies for people who suffer from oxidative stress?

A It depends on what you mean by recommended. If you mean are there alternative medicine sources? Are there health food store sources? Yes.

There are only one or two that established medicine would recommend, but we have natural mechanisms in our body that try to overcome these free radicals, these oxidative stress phenomena.

Q All right. Let's go to the next slide, No. 19.

A I think you want 20. Is it 20?

Q Slide 20. I have a different numbering system.

A This is taken from the *Journal of Science*. I find diagrams and figures much more instructive than numbers and tables, all right, and so let me just point out to you some of the genetic terms of inversion, insertion, deletion and copy number variation.

If you look at the lower right-hand corner

of this slide you'll see the reference. We have a gene A, B, C. That could even be three different parts of a gene, or this whole thing could be a chromosome. It doesn't matter. We're talking about genetic information now.

Now, what is normal is the reference A, B, C. When an inversion occurs it means C, for example, will be put before A rather than after B. This does happen. Chromosomes are known to have this happen to them, and disease are known to be caused by this.

An insertion is when some extra genetic information or extra DNA information is inserted, as you see with the letter D for dog in the second to the right. Below that is deletion, which is quite obvious. In this case we've taken B out.

Then of course copy number variation is again another known cause of a number of disorders, and here you see we've put in -- the person who put this diagram together or figure together for *Science* added four copies of C rather than one copy of C.

Q All right. Let's go to Slide 21.

A Again at the IOM forum, Lipkin, a very good scientist from Columbia University: To emphasize that our working model for autism is one with three dimensions where a genetic susceptibility,

environmental triggers and temporal contacts act in concert to cause disease. It's not just genetics.

Q And again the blue is not your opinion?

A Yes.

Q That's the opinion of the scientist presenting at this IOM conference?

A Exactly. Exactly.

Q Okay. Let's turn to mercury toxicology then.

A A brief review of mercury toxicology. Next?

Q Slide 23.

A This shows the influence of the mother and other sources for mercury exposure of infants. In the mother we have methyl mercury from fish. We also have methyl mercury from chicken. Now, some of the Respondents did not realize that or forgot what they had learned earlier.

The next slide, which please don't show yet. The next slide will give just one reference to the showing that there is methyl mercury in chickens. There is methyl mercury in chickens because this country imports chopped up or pulverized fish bones and pulverized fish products to feed the fowl.

I did a study. The Government of Chile asked me to go down and look at some people. One time

we did a very large study of arsenic exposure. I saw this huge mound by the port, and it was probably the height of a 10-story building. I asked my host what is that? He said oh, that's chicken feed that we are going to send to America.

I said but what is it made of? He said oh, that's our waste products, stuff we don't want, the fish bones and other things that are ground up. This is where the methyl mercury in chickens in this country come from. There are many papers dealing with this. They're not read very often.

We have mercury from amalgam, from the mother's amalgams. We have thimerosal ethyl mercury from vaccines that the mother may have had. These forms of mercury all can pass the placenta and get into the fetus.

In addition, a child from the mother will get thimerosal, especially if the child is being breast fed. The child will get thimerosal ethyl mercury from its own vaccines. They will get methyl mercury from breast milk, methyl mercury from fish, methyl mercury from chicken, methyl mercury from amalgams of the mother and of course the vaccines that the child has been given if the child was given vaccines containing thimerosal.

Q Is it fair to say, do you think, that virtually all children born in the United States have some exposure to mercury whether they get it in vaccines or not?

A I think that's correct. I think that's absolutely correct.

Q And that load can vary from region to region and diet to diet?

A That's correct. When I referee journal articles some new investigators will say this mercury-free human or this mercury-free animal, and what we'll always say is what is the evidence they're mercury-free? No one can really give that evidence. There's always some of this in us.

Q Okay. Then on the next slide you give your reference.

A This is just one of many references.

Q Okay. Slide 25.

A Okay. Again, I must apologize for reading this or reading many of these slides because if I were giving my expert opinion I could extemporaneously say this.

There's nothing more boring to a student in a university than to hear a professor reading a lecture, but I think it's essential that I read it so

that you know the exact words that the peer reviewed expert -- not me -- is saying. If we were in the university setting I could throw in some dirty jokes, but this is not allowable here, of course, just to brighten things up.

Q Well, in this one you're quoting one of the Respondent's experts, right?

A Pardon?

Q In this one you're quoting one of Respondent's experts?

A Yes. Yes. Anyway, here we go. This is Clarkson, again a good friend of mine. I've entertained him in my home with his wife. Tremendous respect for the man. We both get along very well, even though he's Respondent's.

Classification of Mercury Species or Forms. The mercury species are sometimes classified chemically as inorganic and organic. The inorganic would include by this chemical classification elemental mercury, which is Hg^{0}, in the form of a liquid or the vapor; mercuric mercury, Hg^{+2}; and mercurous mercury, Hg^{+1}.

Elemental mercury, Hg^{0}, exists in liquid form at room temperature. Vapor from the liquid, which we call mercury vapor, is more hazardous than

the liquid form. The liquid form has very little, if any, toxicity if it gets into the stomach, for example, but the vapor is different.

The toxicological classification of mercury compounds used by many toxicologists is based on their toxicological properties, and here we break them down into elemental, inorganic and organic. In this classification, although elemental mercury is inorganic, it is put into a separate category because of the many different toxicological properties.

Q If you swallow liquid mercury it basically passes through without being absorbed, true?

A Essentially. There are many cases in the literature, interesting cases. They used to put mercury, liquid mercury, into tubes when they wanted to block the exit from the stomach. They would put the mercury in there to give it some weight. It would go down, and it would block anything from going out of the stomach.

There are a number of cases when the balloon broke and they had mercury there and it stayed there for quite some time or stayed in the intestines. There were absolutely no toxicological effects. Many, many papers in the literature deal with this.

Q Whereas as you say, if you inhale elemental

mercury vapor then you can have toxicological effects?

A Yes. If you inhale elemental mercury the vapor is very quickly taken up in the lungs. It passes quickly into the blood, is transported very rapidly to the blood-brain barrier.

Since it's lipid soluble it needs no special mechanism. It just diffuses across the blood-brain barrier and gets into the brain where it's converted to mercuric mercury very quickly.

Q Okay. I guess we've covered everything on that slide.

A I think so.

Q Let's go on to Slide 26.

A Exposure at toxic levels to inorganic mercury usually occurs in an occupational setting and is not a danger to the general public. This is still the statement of the experts. Now comes my statement in red. This statement deals with external exposure, not endogenous inorganic mercury production in the body.

It's different if the mercury production is in the brain. If the mercury from methyl mercury is demethylated it gives mercuric mercury, and then it becomes a real problem. The organic species of mercury would include methyl mercury, thimerosal,

ethyl mercury and some phenylmercury compounds, all of which we know quite a bit about.

Exposure. The major source of mercury vapor in the atmosphere is a natural degassing of the earth's crust. The atmospheric mercury is distributed globally and eventually is converted to a water soluble form and returned to the earth's surface by rain.

Methyl mercury in fish is found in a water-soluble, protein-bound form. Inorganic mercury is also found in food. The sources are known, and it does not amount to very much.

Next slide, please?

Q Slide 27.

A Mercury vapor emitted from dental amalgam is the main source of mercury vapor affecting the general public. In fact, mercury vapor emitted from dental amalgam is the main source of mercury exposure to the general public. Mercury levels in the general atmosphere and in drinking water are so low they're not important.

Deposition and toxicokinetics, elemental mercury, swallowed liquid mercury, is only slowly absorbed from the GI tract -- we said that -- and is generally of no toxicological significance.

Mercury vapor is readily absorbed from the lungs. The mercury becomes dissolved in the blood and diffuses to all the tissues in the body. It is highly diffusible and lipid-soluble.

Q Let me ask you a question about coal-fired power plants. Do they release mercury into the air?

A They do. As far as the mercury in the general environment is concerned, something like 70 percent of it comes from coal-powered utility plants.

Q Excuse me. It's not distributed equally all around the area of the plant, is it?

A No. It's highly concentrated. The closer you are to the plant the greater the amount of mercury that you're going to inhale, but I think Landrigan showed in his El Paso study by the time you get a mile away from the plant the concentrations were quite low.

Q And what form of mercury is that that comes out of the coal plant?

A Elemental mercury. Elemental mercury.

Q In vapor?

A In the vapor form, yes.

Q Yes.

A Primarily. Deposition and toxicokinetic. We've gone through most of that.

Q Yes. Let's go to Slide 28, I think.

A Again continuing with Goyer and Clarkson's chapter, mercurous mercury exposure is rare, but it happens in, for example, pink disease. These compounds have a low solubility in water and are poorly absorbed from the GI tract. In certain cases the compound or the mercurous mercury can decompose to Hg^{0} and one atom of Hg^{+2}. Very little is known regarding disposition of mercurous mercury in the body.

Now, mercuric mercury is a real culprit. Absorption from the GI tract of mercuric compounds in food for humans is about 15 percent, whereas for methyl mercury it's 90 to 95 percent, if not higher. There's also a difference in the distribution between red cells and plasma.

For inorganic mercury, the ratio of cell to plasma is two to less than one, but for methyl mercury it's 10, so there's 10 times more found in the red cells or in cells in general than in plasma. Therefore, 10 times more mercury in red blood cells than plasma.

After exposure to mercuric mercury or mercury vapor, the greatest concentration of mercury is in the kidneys. Methyl mercury has a greater attraction to the central nervous system, especially

the posterior cortex.

Q The posterior cortex meaning the back of the outside of the brain?

A Yes.

Q Okay. Let's go to the next slide, No. 30. Excuse me. No. 29.

A Yes. I think just the last sentence here is probably worth taking the time to read. Dental amalgam. Fillings in girls and women of reproductive age should be used with caution to avoid increased prenatal mercury exposure.

Q And again this isn't your opinion. This is a published opinion?

A Everything in blue is the opinion of a published expert that I've taken sometimes word for word from a published article, a peer reviewed article.

Q Okay. Now, earlier in opening I showed the Special Masters that series of five papers that came out of Seattle on the adult monkeys. Have you prepared some slides about those studies?

A Yes. It may begin with the next one. I'm not sure.

Q I think it is.

A Yes. Okay. This is one of those papers by

Vahter and Burbacher is also. There's a list of distinguished authors of this set of papers.

Monkeys were given methyl mercury for six, 12 or 18 months orally or mercuric chloride continuous for three months. I want to be certain that we understand that in these studies a subtoxic dose was given because we're going to talk about eventually the difference in mechanism between a subtoxic dose and a toxic dose or a small dose via a large dose of methyl mercury and the different mechanisms that are probably involved.

It took about four months to reach blood steady state. The blood total mercury elimination, $T_{1/2}$, was 26 days. The blood inorganic mercury, which was primarily mercuric mercury, was about seven percent of blood total mercury.

Brain inorganic mercury, again primarily mercuric mercury, was nine percent of total brain mercury at six to 12 months and by six months after exposure had stopped. Six months after exposure had stopped. Seventy-four percent of the total brain mercury in these monkeys was inorganic mercury.

Q Let me stop you. Let's explain what is total mercury versus its component parts in these kinds of studies.

A Yes. When these people used to do an analysis by a now relatively old-fashioned technique at the time, absorption, they would measure the total mercury, and that's inorganic mercury plus organic mercury. Then they would measure I think -- it slipped my mind. Let's say they would measure inorganic mercury, and the difference between inorganic and total would be organic mercury.

These are old studies. Today we do it entirely different. These studies in the old days would take weeks to get the answers, whereas we have the basic equipment in my laboratory. We could do in less than one day what they did in a month.

Q Yes. What I'm trying to make sure we get across is that if the Special Masters see a term total mercury, that would include both organic and inorganic, right?

A Yes. Yes. Absolutely.

Q And if it's inorganic or organic it would be specified as one or the other?

A Yes. Yes.

Q Okay.

A Yes.

Q Now, you were explaining that in the group of monkeys that were fed methyl mercury for 12 months

and then they stopped feeding them and then waited six more months before they sacrificed them and looked at their brains, their inorganic mercury continued to go up in percentage, right?

A Exactly.

Q Why was that?

A Because the methyl mercury was slowly demethylated to mercuric mercury, and mercuric mercury cannot pass the blood-brain barrier either way to any great extent.

That mercuric mercury, almost every first year biochemistry student knows if you want to inhibit an enzyme and you don't know what to use, if you use mercuric mercury it's probably going to work because mercuric mercury is a classical enzyme inhibitor, especially if the enzyme has a thiol, an -SH group, in the active center.

If the mercuric ion ties up that -SH group, usually as we'll point out later in a very important paper, the activity, enzyme activity, will be completely inhibited.

Q Now, in this study did these investigators try to estimate the half-life in the brain of that mercuric mercury?

A Yes. Let's see. Where is it here? Yes.

The brain inorganic mercury elimination, $T_{1/2}$, was a matter of years. I mean, methyl mercury got out in a matter of weeks or months, but there are some people that think it's not a matter -- it's many, many, many years.

I'll tell you at one point where a number of studies have been published where a farm animal ate a methyl mercury fungicide, one in New Mexico. It was in a Coke bottle. He tipped it over and lapped it up. Two days later the farmer killed that animal and fed the meat to his children. One child died quite soon. Another one lived until she was 21 years of age.

At 21 years of age, at the autopsy they took the brain out and did a mercury analysis. The inorganic mercury at that time, in fact the total mercury, was 100 times above normal, and most of it was inorganic mercury, so inorganic mercury really stays in the brain a long, long time.

Q Is that evidence that what happens in humans is similar to what happened in these adult monkeys?

A Absolutely. Absolutely. Absolutely.

Q The methyl mercury can transfer into the brain past the blood-brain barrier?

A We know. We know this from the Clarkson studies in Iraq. We know it from the Minamata studies

in Japan. We know it from many studies in animals that methyl mercury will form a bond with amino acid cysteine, and that molecule, that cysteine methyl mercury molecule, looks like another amino acid called methionine.

This cysteine methyl mercury compound will be taken up by the methionine transport carrier protein, and it will get methyl mercury into the brain that way.

Q Once the methyl mercury is in the brain it can come back out again too, can't it?

A Pardon?

Q The methyl mercury can come back out again?

A It's a much slower mechanism, and we really don't know what that mechanism is. Some of us think that it's because of being bound to glutathione, but the mechanism, as you can see, or the half-time is -- let's see.

The brain inorganic mercury half-time is a matter of years, as we say. No. We want the methyl mercury half-time. It's around here someplace.

Q I know it's in the paper.

A Yes. It's someplace in here. I'm sorry. I thought we had it here.

Q We may have that on another slide.

A It's a matter of 30 or 40 days, maybe 50 days.

Q Okay. So the methyl mercury half-life in the brain is 30 or 40 or 50 days, which would mean after a year or so it's essentially all gone.

A A lot of it is gone, yes.

Q Whereas the inorganic mercury that's produced in the brain by the breakdown of methyl mercury, that stays there for years?

A That stays there for years.

Q Let's go to Slide 31. This is still the same paper from Dr. Vahter, right?

A Yes. It more or less points out --

Q Well, this is what I was just asking you about.

A Yes.

Q What does it say? After it estimates the half-times in blood of 50 to 80 days, what does it say then?

A In human subjects exposed to methyl mercury, mean half-time in blood of 50 to 80 days with considerable variation between individuals have been reported. They give the references to this.

The high blood mercury level in heavy individuals indicate methyl mercury is distributed to

fat to a limited degree, so if you don't have very much fat it gives rise to a higher dose of methyl mercury per lean body weight.

In other words, if the methyl mercury doesn't go into fat because there's less fat around, there's going to be more methyl mercury in the blood and more methyl mercury going in the tissues.

Q Some of these monkeys in the study were especially heavy, right?

A Yes.

Q And in those heavy monkeys they were still basing the dose on the total body weight, right?

A Yes.

Q So they got more methyl mercury than the lighter monkeys, but their blood level got much higher, right?

A Yes.

Q And why is that again?

A Because in those animals with less fat then the blood level is going to be higher because there's not enough fat for the methyl mercury to go into from the blood.

Q And then you have another paper here cited by a Swedish author.

A Yes. It just points out again that dietary

lipids affect whole body retention and relative organ distribution of methyl mercury and inorganic mercury. It means that diet is important.

Q Another variable in how much mercury --

A Another variable. Yes, sir.

Q All right. Slide 32. What was the point of this paper?

A All right. This is a very recent paper, year 2008, a very important paper.

When you talk to most people, even those with experience in mercury research, and you ask them what does mercuric mercury do to the brain -- we know it's there; what does it do -- most people will say well, it ties up sulphydryl groups.

What does that mean? Well, there are sulphydryl groups in proteins. Can you be more specific? Well, they'll say what do you mean? Being an enzymologist I'll say what enzyme specifically is methyl mercury or is inorganic mercury, mercuric mercury, inhibiting in the brain?

There have been very few good studies along these lines for a variety of reasons until this study came out. Now, in this study they took a thioredoxin system. Now, they were able to use enzymes that were made by DNA recombinant technology so there's no

contamination with other enzymes.

One of the axioms of enzymology is don't waste clean thinking on dirty enzymes. Don't waste clean thinking on impure enzyme fractions. Recombinant DNA enzymes are very, very pure. You don't have to worry about contamination there.

And so essentially what they showed here was that, first of all, let me say the thioredoxin system is critical for cellular stress response, protein repair and protection against oxidative stress. Mercuric mercury or mercuric chloride, which contains mercury chloride, and methyl mercury inhibited recombinant rat thioredoxin reductase with IC_{50}. That's the concentration that would cause inhibition of 50 percent of the activity, so that's a quantitative term, the IC_{50}.

It had IC_{50} values of 7.2 and 19.7 nanomoles respectively. That means that mercuric mercury was more inhibitory than methyl mercury. Overall mercury inhibition was selective towards a thioredoxin system. The latter system consists of thioredoxin reductase, which has selenol cysteine in its active center and thioredoxin, which are widely distributed in the main organs and tissues and are also synthesized in nerve cell bodies and transported to synaptic terminals.

Fully reduced human thioredoxin bound mercury and lost all five free thiols and lost activity after incubation with mercuric chloride or methyl mercury, but only mercuric chloride generated dimers. These dimers were very stable and very inhibitory.

Q Now, is the mercuric chloride going to break down in this system into Hg^{++}?

A Momentarily you must say, but I think I have a slide. It may be the next one. It's the next one. We'll get back in just a minute.

Q Yes. You're right. The next slide does discus this. Let's go to 33.

A We can wait. Let me just say that you asked mercuric chloride breakdown. Yes, it does break down, but we don't have free mercury ions or free arsenic ions or free metal ions floating around in the blood, the plasma or in cells.

They are attached very quickly to sulphydryl containing compounds like glutathione, like cysteine, another -SH containing amino acid, and also proteins that have -SH, have cysteine, either in the active center or in the outer structural part, so it breaks down, mercuric chloride, to mercuric ion. That mercuric ion is very quickly bound to something, so

there's no free mercuric ion floating around for two or three days.

Q Is this the same type of mercuric mercury that we talked about in the adult monkey studies that's left in the brain?

A Yes, it is. Yes, it is. Now getting back to this. In particular, the remarkable potency of the mercury compounds to bind to selenol-thiol in the active site of thioredoxin reductase should be a major molecular mechanism of mercury toxicity.

I was the author of a chapter on the toxicology of methyl mercury in I think it was the year 2000 National Research Council monograph that was written, and I wish we had that sentence because at that time we could just say mercury tied up an -SH group.

Here it says: In particular, the remarkable potency of the mercury compounds to bind to selenol-thiol in the active site of thioredoxin reductase should be a major molecular mechanism of mercury toxicity. I agree 100 percent with these authors.

Q And this was new information just this year?

A Year 2008. I think it was last month. It was just published. The page number just came out within the last week. It was prepublished and put on

the web first.

They also performed human tissue culture studies and lysate studies, and now I want to say in my own words the results of this research are very pertinent and important. The thioredoxin system is of course in the brain and most tissues. It appears to be uniquely sensitive to mercuric mercury and methyl mercury. It is unfortunate the ethyl mercury was not investigated in this system.

Q All right. Now we want to talk a little bit about the different forms of organic mercury here.

A The next slide, please?

Q Slide 35.

A This is the chemical formula for thimerosal. If you look at the left side of the molecule it says CH3. You'll see mercury. The bond between the mercury and sulfur is cleaved very quickly in the body. It's metabolized very quickly to yield ethyl mercury. It's this ethyl mercury that does most of the traveling in the blood and gets across the blood-brain barrier.

The next slide, please? I don't know whether it's necessary to read all of this. It points out the difference in solubility. Ethyl mercury has a solubility of 1.4 times 10 to the minus four grams per

100 milliliters of water, and that can be compared to not one gram per milliliter of water, but 100 grams of thimerosal per 100 grams of water. A tremendous difference in the solubility.

Next slide?

Q When thimerosal or merthiolate was formulated, why were they interested in having a soluble form of mercury? Is that part of its preservative stance?

A Let me stop for a second. Merthiolate, which is also thimerosal, breaks down to ethyl mercury. No one really knew at the time. It was claimed that thimerosal and/or merthiolate was bacteriostatic. It would stop the growth of bacteria.

But in the latest slide I'll point out what the FDA now says about it; that that isn't necessarily so. Can we have the next slide perhaps?

Q Yes. Slide 37.

A So thimerosal is rapidly metabolized to ethyl mercury. The statement is taken from one of Tom Clarkson's articles.

Q Okay. And then the next slide, 38?

A Here we go. Ethyl mercury or methyl mercury do not just float around free in body fluids and cells. They have a high affinity for binding to and

are transported via thiol-containing compounds such as glutathione, cysteine and cysteine-containing proteins.

Q What does thiol mean?

A It's an -SH group. It's a radical. It has a valence. It can form a chemical bond with carbon compounds, carbon atoms.

Q And the S in the -SH is sulfur?

A S is for sulfur. H is for hydrogen. The hydrogen is very reactive. It will come off very quickly, especially in the presence of oxygen or something like mercuric mercury or methyl mercury, which will react with it very quickly.

Q Okay. All right. The next slide, Slide 39?

A Now, the safety and efficacy of thimerosal have been questioned by the FDA as shown in the following slides.

Q Okay. Slide 40?

A Slide 40 states, and this is now from the *Federal Register*: Rule will be based on page 11 of the *Federal Register* 436 published January 5, 1982, which states: The panel concludes -- this is an FDA panel. The panel concludes that thimerosal is not safe for over-the-counter topical use because of its potential for cell damage if applied to broken skin as

allergy potential.

More importantly, in my opinion, but it states here, it is not effective as a topical antimicrobial because its bacteriostatic action can be reversed. I'm going to make this comment, but it's really one that Congressman Burton made once on a committee that I was involved in. He said: If they did not think it was safe enough to apply topically to adults, what evidence did they have for its safety for injection into children?

The next slide, please? This is again in the *Federal Register*. A ruling came out by the FDA. It came out October 11, 2005. It's effective April 1, 2007, about a year ago, and I quote:

A number of active ingredients have been present in over-the-counter drug products of various uses as described below. However, based on evidence currently available there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified use.

Now, there are about 200 compounds that they list in this *Federal Register*, and one of them, thimerosal, was quoted as one of these ingredients.

Q Okay. Now let's go to some studies about

what happens to thimerosal in infants.

A The major studies in infants -- not all of them -- have been done by Pichichero from the University of Rochester. I think, but I don't remember whether Clarkson is one of the co-authors of these papers.

It deals with mercury concentration and metabolism in infants receiving vaccines, and essentially they gave to infants age six months and younger vaccines that contained thimerosal. They list the vaccines. The first group received vaccines containing thimerosal, but then 21 control infants received thimerosal-free vaccines that were available.

They state: We obtained samples of blood, urine and stools three to 28 days after vaccination. Estimated blood half-life of ethyl mercury was seven days, although they changed that number in a subsequent number.

Their interpretation? Administration of vaccines containing thimerosal does not seem to raise blood concentration of mercury above safe levels in infants. Ethyl mercury seems to be eliminated from blood rapidly via the stools after parental administration of thimerosal in vaccines.

My comment: This sample size is highly

unlikely to capture the full range of human variation in handling mercury exposure.

The next slide, please? This is the 2002 paper, the same paper. This shows you some of the variation. Now we're plotting blood mercury in nanomoles per liter versus days since the last vaccine. The dark or the triangles -- I think they're called diamonds -- are for infants of age two months, and six months are shown by the squares.

As you can see, in one case, the very high one, you have 20 nanomoles of mercury per liter of blood, and in other cases you're down to almost 2.5 so you almost have a tenfold -- almost a tenfold -- variation in how children respond to injections of vaccines containing thimerosal.

Q Now, this was on 40 infants. If you had done this study on 4,000 infants would you expect the range to be even wider?

A Probably. Probably. From everything that we know that we've seen, I think it would be much wider. We'd have much more.

Next slide? This is in the most recent or more recent Pichichero paper done in Argentina with newborn infants in this slide. This is now a time course, days since the last vaccination, and again you

see the huge variation, anywhere a little above zero to eightfold or eight nanograms per mil. There's variation. You've got to expect that in children or almost any human as far as the way they handle mercury.

Q Even at 30 days after vaccination, there was still a range of values for them.

A Yes. Yes.

Q Does that show that not all children will process the mercury as fast as others?

A I'm sorry?

Q What does that show about the children if the range varies at 30 days?

A Well, they're processing it differently because they probably have some difference in their metabolism, which may be genetically determined.

Q Okay. Let's go to the next slide.

A This again shows the same sort of thing in two month old infants, and again you'll see the variation is anywhere from a little bit above zero to five nanograms per milliliter here. Again there's variation.

Out at the end at 30 days since the last vaccination you're almost as bad as you were at the very beginning with a very high outlier, again showing

that individuals handle mercury differently. There's no set response.

Q Okay. And then the next slide, please?

A Again it shows the six month old infants. So you're getting variation all the time no matter how old the kids are. You're getting variation. Here it's between zero and five at the beginning.

Q Okay. Slide 48. This is still the Pichichero 2008 paper, correct?

A Yes. What did we want to say about this? Oh, yes. In the earlier paper, the 2002 paper, these same authors claimed that the blood half-time for the mercury was seven days. Now for some reason or other they've cut it down by half to 3.7 days.

Again, this shows the variation not only -- I mean, these studies I think were done in the same laboratory or parts of them were anyway, and it shows the variation that can occur when you're measuring mercury and/or a group of people responding differently to mercury.

It's amazing that it took 30 days for blood mercury to return to prevaccination levels, so when you say that mercury leaves the body very quickly after vaccination to me in the life of an infant 30 days is a long time.

It was addressed, as Pichichero himself states in this paper, that some methyl mercury was detected in all the blood samples of the young children.

Q So they had some background methyl mercury exposure too?

A Yes.

Q If they had a difference in processing ethyl mercury, would you expect a difference in processing methyl mercury? Would that be independent?

A Based on what we know, both of them would be demethylated. That's about the major similarity that I would venture at this present time. Ethyl mercury would be demethylated to mercuric mercury, and the methyl mercury would be demethylated to mercuric mercury.

Q Once the ethyl group or the methyl group is taken off of an organic mercury compound what's left is the same thing, right?

A Yes. Absolutely. Absolutely.

Q Hg^{++}?

A Hg^{++}, which is going to react with something very quickly.

Q Okay. Slide 50? Wait a minute. We didn't finish Slide 49. I'm sorry.

A We should make a note that as far as now it's my opinion. These were supposedly normal children that Pichichero dealt with. They were not autistic children -- they were too young -- or they were not autistic prone children who may process mercury in vaccines differently.

No mass balance data was given. By mass data I mean if you give 10 milligrams of something to a human being you want to know where that 10 milligrams went to. You either want to find 10 milligrams in the urine and the feces, or if you don't find the 10 milligrams, you find only five milligrams in the urine and feces, then you're going to say there's five milligrams that stayed in the body someplace.

The next question would be where did those five milligrams go? In this case they don't know. How much thimerosal ethyl mercury was given is known, but what percent of the dose was eliminated was not stated and experimentally could not be determined because of the protocols they used.

How much ethyl mercury stayed in the brain or in other tissues? They don't know. They didn't try to do that. The authors state they were unable to determine the fate of the mercury after it leaves the

blood. They're now talking the mercury that came from thimerosal. No mercuric mercury was determined.

The paper is flawed, and I think the next slide -- yes. Now, this is an independent evaluation. The *Pediatrics Journal*, which does not take letters indiscriminately. The letters to the editor that you send in to the *Pediatrics Journal* are peer reviewed and then published if the editor thinks they're worth publishing, so the citation really is *Pediatrics* post publication peer reviews, March 30, 2008.

Dr. Indech discusses invalidating assumptions of the Pichichero paper, and I quote: While the methodology admits the underlying assumption that lowered levels of these chemicals result from body elimination of them, perhaps the more rapid decline in measurement levels of ethyl mercury is due to stronger, undetectable binding to tissues in the central nervous system.

The pharmacokinetics of such a process would be identical to that observed, yet such a process may give rise to autistic symptoms whereas total excretion from the body would not. In short, simply because the levels decline you can't make the assumption that the toxin has been eliminated from the body. The paper is

fundamentally flawed. End of quote.

Q In fact, if the same thing happened in these infants that happened in the infant monkeys what would you expect? Would you expect some of this mercury to end up in the infants' brains?

A Absolutely. No question about it. I think Burbacher did show that the thimerosal injected via vaccines -- whatever he did with the thimerosal. Actually it was direct injection of thimerosal, I think. That much of the mercury did end up in the brain.

Q By the way, are you aware of any way under current technology that you could measure the amount of mercuric mercury in a child's brain?

A A living child?

Q A living child.

A Absolutely there's no way we can do it. I thought we had a way, and I called some people up who are very good with this sort of thing and they said no, no way.

Because there are ways of measuring lead in our bones by putting our forearms in a sort of machine and it will tell you how much lead I have or a child has in his bones. I thought we could use that same thing for mercury in the brain, but they said

absolutely not. We cannot measure the amount of mercury in a human living brain.

Q Because in this trial we're not going to have any evidence directly of inorganic mercury in the brains of these two boys, but is that because nobody could do it?

A You can't do it because they're alive. We have autopsied data where that has been done, as we'll point out later, papers that we'll quote of children, autistic children who died and at autopsy the brains were removed and the mercury, both inorganic and organic mercury, was determined.

Q But you can't do it in a living child's brain?

A Absolutely not. We're not Nazis.

Q Okay. Slide 51.

A Well, in preparation for what's coming: Thimerosal pharmacokinetics obtained -- Pichichero, et al -- using nonautistic children are not the same as those expected from autistic children. The latter appear to have different efflux kinetics as we point out in later slides.

Q All right. And now we're going to go to a discussion of brain concentration of mercury species, correct?

A Yes.

Q Okay. This is a paper from the National Institutes of Health in Bethesda published in the year 2004, a paper that really has withstood the criticism of time, Mercury Concentrations in Brain and Kidney Following Ethyl Mercury, Methyl Mercury and Thimerosal Administration to Neonatal Mice.

The main objective of this study was to define and compare mercury concentrations in the organs of neonatal animals exposed to methyl mercury or thimerosal. The toxicity of these two mercury species in a neonatal animal model is believed to be similar to humans with respect to organic mercury pharmacokinetics.

Q Now, just for purposes of the audience, neonatal means newborn?

A Yes. Yes.

Q Okay.

A For a period of one or two months I think it is.

Q Okay.

A For the mice it would be different. For a short period of time.

Q Okay.

A Neonatal mice seem to be the best rodent

model to study thimerosal disposition in order to closely mimic human exposure. Mice exhibit methyl mercury brain-blood ratios of about one, closer to the three to 10 ratio seen in primates, than the ratio in rats estimated by Magos in 1986.

Again let me point out Magos is a very good investigator of mercury toxicity. I don't know him personally, but he has a superb reputation for doing very good work, but 1986 is different than the year 2004 as these studies were done. Science progresses.

The fact that we no longer think that rats are better to use, that rats are not better to use, is not meant to be an insult to Magos. It's just that times change. We get more information. Magos is a superb investigator. He's one of the Respondent's.

Q Let's stop. I want to have you explain what is this blood-brain ratio they're talking about here or brain to blood I guess it is. Yes. They call it the brain to blood ratio. What does that mean?

A It's the concentration of whatever species of mercury, usually total mercury, you're concerned about, the concentration in the brain versus the concentration in the blood. That ratio is used by some people. I myself never use it. Used by some people as an indication of how the body handles these

mercury compounds.

For example, the reason we don't think the rat is a good model anymore is the rat hemoglobin has more sulphydryl groups that mercury will bind to and stay in the blood than the human hemoglobin and so it makes the science more complicated. We have a confounding factor if we do studies with rat blood.

Q Would you agree that studies on primates would be a better indication of what probably happens in humans than studies on rats?

A No question about it. I think most people would agree with that.

Q They use rats because they're much less expensive, right?

A Yes. And at one time they were the animal of choice for experimental studies, but times change. We learn more as we go on.

Q Okay. I interrupted you as you were going through Slide 53.

A Yes. In mice it was three to four days for a steady state. More than 80 percent of the mercury in hair in this study was found to be in the form of organic mercury. Blood mercury in these mice was found to be primarily in the organic form. They did other tissue analysis.

Next slide? This shows some of the data. Again, some of the data was lacking, but this is a table that I made up using their data. It shows you that .6 percent of the delivered dose of methyl mercury ended up in the brain of these mice.

When they gave thimerosal 0.2 percent and when they gave ethyl mercury 0.39 percent, but much more percentage-wise of the ethyl mercury ended up in the kidney than did in the case of methyl mercury or thimerosal.

Next slide, please?

Q Okay. Slide 55.

A Let's see. For each compound -- thimerosal, ethyl mercury, methyl mercury -- the percent of mercury that reached the brain was significantly more in young mice as compared to mature mice, so in young mice the blood-brain barrier probably is not matured as much as in the older mice.

In all cases, the level of mercury that reached the adult brain following an IM injection was less than 0.1 percent of the total administered dose. When compared to levels at 24 hours, mercury concentration at seven days post dosing were significantly decreased in the blood, while concentrations within the brain and kidney remained

relatively constant.

In this paper they state with references, and this is going to be a matter of disagreement as we go through this paper or as we go through all these talks. In this paper they state with reference that while methyl mercury gets into the brain by diffusion plus active transport of the methyl mercury cysteine complex, ethyl mercury does not form such a cysteine complex and does not get in that way, but diffuses more readily across the blood-brain barrier.

Now, Clarkson will quite rightly say, as he said in his written form, that we don't know how ethyl mercury gets across the blood-brain barrier. It may use the cysteine complex, but as he himself says we don't know. The experiments have not been done.

Q We don't know how it gets across, but we know that it does get across?

A Yes. Absolutely.

Okay. Next slide, please? Now we go on to another study, Zareba, and I think he is from Clarkson's group also. In the blood of neonatal male mice total mercury concentrations after thimerosal were slightly lower than those after methyl mercury, reaching statistical significance only at day one. The rate of decline of blood levels was roughly

similar in both.

In hair, the total mercury content was approximately two times higher in methyl mercury than the thimerosal treated group. In the brain, which we're really interested in. In the brain, organic mercury levels were significantly lower, approximately three to fourfold -- we're talking about organic mercury now -- in the thimerosal group than in the methyl mercury exposed group.

In other words, the organic mercury in the thimerosal group was decreasing much faster in the brain than in the methyl mercury group. This could be due to either its conversion to mercuric mercury or to it being pushed out of the brain.

It goes on to say: Inorganic mercury levels of the brain were similar in both groups except for the first day after exposure. However, in the thimerosal exposed animals, inorganic mercury accounted for a higher fraction, 12 to 22 percent -- notice the variation; 12 to 22 percent of total mercury -- whereas in the methyl mercury group it did not exceed 10 percent of the total mercury.

Q Now, they gave these mice all the same dose, right?

A Yes. Yes.

Q And yet there was almost a twofold variation after one week in how much inorganic mercury was in the brain of the thimerosal exposed mice?

A Yes.

Q Why was that? Why is that? Why is there such a wide variation?

A I guess that's based on the individual genetics of the animal or the human if you're talking about humans. It could be due to difference in susceptibility. It could be due to a different rate of metabolism. It could be due to many factors.

Next slide, please?

Q Okay. Slide 57.

A Again, this is a continuation. For total mercury in the blood for approximately five percent of the dose was similar for ethyl mercury and methyl mercury, but the subsequent fate of mercury in the body differed.

Brain organic mercury was higher for methyl mercury, three to fourfold, as compared to ethyl mercury. Brain levels of inorganic mercury was about the same in both cases, unlike the infant monkey study. There's bound to be variation, variability between species also.

For kidney, inorganic mercury was three to

four times higher for thimerosal than for methyl mercury, which confirms other studies, including humans. Much higher accumulation of inorganic and organic mercury in the liver in the thimerosal mice than in the methyl mercury ones.

It took about three or four days for a steady state to occur, and more than 80 percent of the mercury in the hair was in the organic form. Blood mercury is primarily in the organic form.

Q Now, you referred to Dr. Magos before. There's a paper he published in 1985 that keeps getting cited over and over again. We're going to discuss that now.

A Yes.

Q If you would turn to Slide 58?

A Keep in mind this is a paper published in 1985. Keep in mind that thimerosal was not on the tip of everyone's tongue at that time, all right? Vaccinations were not being questioned with thimerosal in them.

He compared methyl and ethyl mercury by giving them by mouth, so the ethyl mercury is not given by IM, all right, as vaccinations are given. In addition, rats were used. In a later paper they state that mouse is a better model for studying mercury

toxicity than is the rat. We've discussed this before that times change as we get more knowledge.

The authors state that one of the first toxic effects of methyl mercury is weight loss. In this paper they stated that ethyl mercury caused a greater weight loss than did methyl mercury. This is one example of greater toxicity for ethyl mercury from Magos' own paper.

Ethyl mercury is also more renal toxic than methyl mercury. Mercuric mercury can contribute, and he states in this paper and gives evidence. Mercuric mercury can contribute to injury of ganglion cells also.

Q Okay.

A Next slide, please? They go on to state there were little differences in the neurotoxicity of methyl mercury and ethyl mercury when effects on the dorsal root ganglia or coordination disorders were compared.

Parenthetically, one of the problems in the past has been people concentrated on pharmacokinetics or toxicokinetics of thimerosal, ethyl mercury and methyl mercury and did many, many studies with this and so in the literature the statement creeps in that there are vast differences between methyl mercury and

ethyl mercury.

That's not necessarily so. The pharmacokinetics can be different, but the toxic effects in many ways are similar. I'll show this in the subsequent slide that will list all these one by one. The mercuric mercury formed extraneously from alkyl mercury can contribute to the injury of ganglion cells.

The authors also use mercury concentrations, cerebral damage, histochemical visualization as indication of a toxic or lack of toxic effect of ethyl and methyl mercury. These effects or measurements that they used in 1985 are not as sensitive as enzyme activity inhibition as far as the thioredoxin paper that I quoted for the year 2008 earlier in this talk.

In 1985 when this paper was published, neuroinflammation was not examined since the term neuroinflammation -- very shocking. The term neuroinflammation did not appear in the medical literature until the year 1994-1995. I still can't get over it. When I was first told this I didn't believe it.

If you go back to PubMed and do any kind of literature survey, before 1994 you cannot turn up the word neuroinflammation, but now it's a word used all

the time, especially by the Zimmerman group, a very, very good research group at Johns Hopkins University.

Next slide, please? You went the wrong way. Yes. Here we are.

Now, a paper that's quoted very often, Mercury by Ip, et al. Mercury Exposure in Children With Autistic Spectrum Disorder: Case Control Study. I quote: Thus, the results of our cohort study with similar environmental mercury exposure indicate that there is no causal relationship between mercury as an environmental neurotoxin and autism.

This paper is quoted over and over again, and there are subsequent papers that rely on this paper. This article has a major error in it, and I will now point out the error again which appeared in a peer reviewed journal.

Paper by DeSoto and Hitlan, Blood Levels of Mercury are Related to the Diagnosis of Autism: A Reanalysis of an Important Data Step. I wish to emphasize again, Special Masters, this is not my opinion I'm giving you. I'm reading directly from the paper, a peer reviewed paper in *Journal of Child Neurology*.

We have reanalyzed the data set originally reported by Ip, et al. in 2004 and found that the

original P value was in error and that a significant relation does exist between the blood levels of mercury and diagnosis of an autism spectrum disorder.

Moreover, the hair sample analysis results offer some support for the idea that persons with autism may be less efficient and more variable at eliminating mercury from the blood. The underlining emphasis I added, but this is a direct quotation.

Now, the editor of this journal said in a note that he submitted, and I again quote: But as the editor-in-chief of the *Journal of Child Neurology*, it is troubling to note that the article, Ip, et al., has errors not only in the reporting of the statistical findings, but also in something as simple as a listing of the age range of the subjects.

My comment: Please note, the article being criticized is cited on the previous side, the Ip side.

Q Now, let me ask you.

A Yes?

Q This 2004 Ip study that was comparing the blood levels of mercury in autistic kids and nonautistic kids. What they reported initially was there was no difference in the blood levels of mercury. That's been cited as evidence that mercury is not linked to autism by many, many people, right?

A Yes, sir.

Q Including at least one of the Respondent's experts in this case?

A Yes, sir.

Q But in 2007 these people in a peer reviewed paper reanalyzed that data and found that in fact statistically significant was autistic kids had more mercury in the blood, right, so it turns out the study actually shows the opposite of what it was originally published for?

A Yes. Yes.

Q Okay. Let's go to Slide 62.

A So what happens to the organic mercury that enters the brain?

Next slide, please? Now, this one slide are my comments just to bring things in perspective. The literature supports this. Ethyl mercury, methyl mercury and elemental mercury are converted to mercuric mercury, Hg^{++}, in the brain. The mercuric mercury reacts with thiols of enzymes and structural proteins. Thiols and sulphydryls are synonymous terms.

Thus, mercuric mercury is a well known enzyme inhibitor and has been used as a research tool for that purpose for many years. Does it inhibit a

crucial enzyme in the brain; for example, a brain mitochondrial enzyme?

Mercuric mercury also reacts with selenium compounds to form mercury selenide. The latter compound is very insoluble. It has been claimed to be nontoxic because of its insolubility, but this witness -- I was at a small, closed symposia of 20 people that were brought in to analyze the mercury selenide significance, and when people told me that mercury selenide is free of toxicity I asked them what is the evidence for this and they said well, it's insoluble.

I said that's no evidence. Have you done any radioactive studies to show that it doesn't go anywhere but completely out of the body? They said no. Do you have any enzyme studies at low concentrations that would show some biological activity? No. Then why do you say that mercury selenide is free of toxicity; that the mercury is now bound and therefore cannot do anything? The answer is it's insoluble.

For most of the people there, even those people that had worked and heard this before, they were willing to agree that there is not enough evidence. There is no evidence in the literature that shows whether mercury selenide is or is not toxic.

So anyone who in the early literature said well, we see these black spots when we do some analytic studies, and those black spots are mercury and selenium tied up. In those days they used to say before we knew about the mercury selenide what do you mean by black spots being mercury and selenide? What form of mercury? What form of selenide? They said oh, we don't know, but we think it happened. The science behind mercury selenide is virtually nonexistent as far as any toxicity or what its function is in the body.

In regards with which protein or selenium compound mercuric mercury binds, it is accepted that mercuric mercury remains in the brain for a very, very long time. Those are words used almost exactly by Vahter. Also, the inorganic mercury in the brain of the adult monkeys provoked glial activation and astrocyte death.

Q Now you're talking about the adult monkey study from Seattle --

A Yes.

Q -- that resulted in those five papers that I showed in the opening statement, right?

A Yes. Next slide, please?

Q Okay. This is a paper involving examination

of the brains of who?

A These are people in Greenland who eat a lot of fish, and they did a superb study on mercury accumulation in brains from populations exposed to high and low dietary levels of methyl mercury.

Concentration, chemical form and distribution of mercury in brain samples from autopsies. They have a tremendous number. I've forgotten what the end was, but it's in the hundreds if I remember correctly. Their conclusion is this suggests a slow transformation of methyl mercury to inorganic mercury in the brain. The autometallography demonstrable mercury was primarily located in the glial cells.

All right. My comments is that this is a study of humans; that they're looking at human brains at autopsy time of people in Greenland, some who ate a lot of fish and therefore high exposure to methyl mercury and some who ate just a small amount of fish with low exposure. We'll come back to the significance of this later on.

Q But these people, when they died after a lifetime of eating fish they had a lot of inorganic mercury in their brain?

A Yes.

Q And it was in the glial cells?

A Yes. Most of it was in the glial cells, yes.

Q Okay. Slide 65.

A I think we've sort of gone over this before. This is the '94 study. We can go on to the next one, I think.

Q Okay. Yes. We've already talked about this paper on a couple slides.

A Yes.

Q Now, this next paper on 66, this is yet another one of those five studies --

A Yes.

Q -- that came out of the same adult monkey study, right?

A Yes. The major point of this paper is that monkeys' inorganic mercury may be the proximate form of mercury causing changes in astrocytes (support cell growth and are sources of neuronotrophic factors) and microglia, which create neurotoxic agents in the population of cells. Both astrocytes and microglial accumulate inorganic mercury. It just goes on and on.

The loss of astrocytes and increase in activated microglia in the thalamus may have impact on the function and survival of neurons in thalamus after

they've been exposed to methyl mercury.

Q So this monkey study found that the inorganic mercury in the brain which was activating these glial cells could well be creating harmful effects. Is that right?

A Yes. Well, they found that it was concentrated in the glial cells, and we know that mercuric mercury certainly is not the best thing to have in the cell. It can cause a lot of damage.

Q Okay.

A This is another one.

Q Now, the next slide, 67. This is yet another one of those five papers that came out of that same adult monkey study.

A I hate to read the whole thing. Would the Special Master like me to read all of it?

Q Well, let me ask you this. Look at the second bullet point.

In the monkeys that had been exposed for 12 months and then they were left alive for six months with no additional methyl mercury exposure, what happened to their glial cells?

A Seventytwo-percent in the six months, 152 percent in the 12 months and 120 percent in the 18 month methyl mercury exposed group, and the number of

reactive glia in the clearance group remained elevated.

The inorganic mercury exposed group showed a 165 percent increase in the number of reactive glia.

Q One group of these monkeys they fed inorganic mercury to and the rest of them got methyl mercury, and both groups ended up with inorganic mercury in their brain --

A Yes.

Q -- activating glial cells?

A Yes.

Q Okay. Let's go to the next slide.

SPECIAL MASTER HASTINGS: Let me make a comment.

THE WITNESS: Yes, sir.

SPECIAL MASTER HASTINGS: Actually, people in the audience were chuckling at my facial reaction to your question, Dr. Aposhian, whether I wanted you to read all of this particular slide. The answer in general is no, I don't have any particular desire to hear you read things.

What our hope here was we wanted expert reports in written form. We would sit there and read it in our offices, and then the oral testimony is where you would get into emphasizing what's important

there or go over nuances or answer questions that we had about the written, but I think in general just reading everything you've got here doesn't do us any good.

THE WITNESS: All right.

SPECIAL MASTER HASTINGS: We can read.

THE WITNESS: Okay.

SPECIAL MASTER HASTINGS: Go ahead, Mr. Williams.

BY MR. WILLIAMS:

Q Okay. Well, let's look at this Gallagher paper for a minute, and let me try to ask you what's important about it.

This again is a 1982 paper, and it's looking at the structural effects of mercuric chloride and methyl mercury. Now, mercuric chloride. Again, is that a way to deliver inorganic mercury to these animals?

A It is a way of delivering inorganic mercury to animals.

Q Mercuric mercury. Right.

A Pardon? And directly into the brain. These are injections directly into the brain, okay?

The major point is that in spite of the distinctive clinical syndromes in these two classes of

mercury compounds, mercuric chloride and methyl mercury have, they are capable of inducing neuronal necrosis in the brain.

Q Because some of the Respondent reports suggest or claim that inorganic mercury is harmless in the brain, that it's sequestered there and it's okay for it to be there, right?

A That's what some people think.

Q Is this paper consistent with that view?

A It's not consistent because when they injected the mercuric mercury directly into the brain they got a neuronal necrosis and so it's a direct effect of the mercuric mercury.

I want to apologize to the Special Masters. I thought evidential toxicology would be a different way of doing it. I suppose I should have given the usual spontaneous rendition.

SPECIAL MASTER HASTINGS: Well, you need to do whatever way you feel is more explanatory.

THE WITNESS: Okay.

SPECIAL MASTER HASTINGS: I'm just telling you that it helps us for you to tell us what in here is important.

THE WITNESS: Okay. Fine. Okay.

//

BY MR. WILLIAMS:

Q Okay. Let's go to Slide 70, please. Now, this is a very recent paper reviewing the role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. We've heard you describe thiols as being the sulfur hydrogen groups.

A Yes.

Q They're on many enzymes, right?

A Yes.

Q Dithiols are just two of them?

A That's two of them, yes.

Q Okay. And what are ligands? What are interacting ligands?

A That's something that they would react with, what the metal would bind with.

What's important in this slide is that for short-term -- they're discussing short-term high dose -- that there have been studies with high doses and low doses of methyl mercury, and they point out for short-term high dose methyl mercury toxicity as used by Magos in 1985 the approximate toxic agent is most likely methyl mercury itself due to the high dose delivered resulting in a direct toxic effect before demethylization of the methyl mercury occurs.

However, for chronic low dose like those

five studies that we've discussed from Seattle -- the Charleston, the Vahter studies -- in those low dose exposures by Charleston and Vahter the proximate toxic agent is most like inorganic mercury due to both on the one hand its long-term accumulation in the brain and extremely long half-life therein.

I think this is a very important paper in pointing out the differences between high dose and low dose methyl mercury.

Q And this paper also concludes that the result of that adult monkey study showed that inorganic mercury was a toxic agent in the brains of those monkeys, right?

A Yes.

Q Can you say yes out loud?

A Pardon?

Q You just nodded your head.

A I'm sorry. Yes.

Q The court reporter didn't hear that.

A Yes. Yes. Yes. I'm sorry. My apologies.

Q Okay. Now, did you make an overall slide that compared methyl mercury and ethyl mercury?

A I think -- I hope -- it's the next one.

Q I think it's No. 71.

A Okay. Yes. All right. I sat down and

thought of information. I wanted to try to compare these because again and again I was so wrongly impressed with everyone saying these two compounds, methyl mercury and ethyl mercury, are so different.

But what everyone was describing early in the game were the pharmacokinetics are different. They really had no evidence that the toxicity was that different.

Q And by pharmacokinetics you mean what?

A What happens, how rapidly the blood level goes up or down, how it's distributed, where it goes in the body. Pharmacokinetics and toxicokinetics deal with numbers, the quantities expressing what happens to a compound in the body essentially in quantitative terms as to where it goes, not necessarily what its toxic effects are. Pharmacokinetics usually deal with numbers rather than symptoms. Usually. There are exceptions.

So here we have a column for methyl mercury and ethyl mercury. Both of them are organic mercurials. Both of them induce neuronal necrosis, and the references to these are in the slides. If I added the references in every case it would be a very cumbersome slide.

Metabolized to mercuric. They're both

metabolized to mercuric mercury. Cause weight loss, Magos, et al. in 1985. Cause less weight loss, methyl mercury. Ethyl mercury causes greater weight loss, which is one of the first signs of organic mercurial toxicity.

Less renal toxicity for methyl mercury. Greater renal toxicity for ethyl mercury. There was little difference in the neurotoxicity of methyl mercury and ethyl mercury on the dorsal root ganglia or coordination disorders according to Magos, and the same thing was true in the methyl mercury column.

Toxicokinetics. Different than ethyl mercury in normal children or infant monkeys. Methyl is different than ethyl. In the ethyl mercury column toxicokinetics are different than methyl mercury in normal children or infant monkeys.

The brain inorganic mercury level is lower and persistent. The main thing is it's lower from methyl mercury. Methyl mercury doesn't stay in the brain long enough to get as much inorganic mercuric mercury. The brain inorganic mercury level is higher and persistent for ethyl mercury. It probably is because ethyl mercury is converted much more rapidly to inorganic mercury in the brain than is methyl mercury.

Brain organic mercury level is higher, but temporary. Brain organic levels for ethyl mercury is lower, but temporary. Frequency of human cells with chromosome aberrations. Not significant for methyl mercury. They are significant for ethyl mercury.

Oral exposure versus IM exposure. Methyl mercury can cause cerebral palsy and mental retardation. It can cause autism. Ethyl mercury can cause autism. Methyl mercury crosses the blood-brain barrier using the methionine carrier protein, and the ethyl mercury crosses the blood-brain barrier by diffusion and/or other means.

Q Okay. Let's go on now to a brief discussion of how all this relates to biology and autism.

A All right.

MR. WILLIAMS: Go on to Slide 73, Scott.

THE WITNESS: Okay. This is a slide from Dr. Swedo from the NIMH. I like this slide. I like colorful things anyway.

Idiopathic means we don't know, so although we have a small number of cases of autism that we know have a genetic defect and we have a small number that are teratogens, let me just say for the Court a teratogen in the dictionary will say a teratogen chemical causes monster formation or abnormal

childbirth.

Teratogens have an effect in utero. By definition, they only affect an embryo once the egg has been implanted, whereas a mutagen reacts with the DNA and can occur before implantation. So teratogens have their action in utero.

The next slide? The pathogenesis of autism, again from Dr. Swedo. We have a genetic defect which will cause a neuronal dysfunction and damage and will give autism. Now, each one of these colored ellipses I guess just have a few words in them, but there's a tremendous amount of work to be done in elaborating each one.

The next slide, please? This is a plausible pathway for ethyl mercury toxicity. It's built on one that we showed in the Cedillo trial, but we've changed it to some extent here.

BY MR. WILLIAMS:

Q I think the changed one is 76.

A Yes, I think you're right.

Q I think this is the one from Cedillo.

A Yes. Let's go to 76 then. This one was supposed to be -- here we are.

So here we have thimerosal, ethyl mercury. This ethyl mercury will be converted to mercuric

mercury in the brain. That can cause neuroinflammation. It can have an effect on developmental windows of various organs in the body in the child. You have neuroinflammation going on to encephalopathy and regressive autism.

We bring in hypersusceptibility here as we pointed out or will point out in I think a subsequent slide, the Woods study that shows at least 15 percent of the population handles porphyrins or mercury has an effect in changing the porphyrin excretion and porphyrin metabolism.

Next slide? Okay. What's important here? We know there's a brain growth phenotype in ASD, and inflammatory response has also been described in other parts of the brain. We have the decreased cellular Purkinje neurons and cerebral cortex changes that have been reported by many investigators.

Next slide?

Q Now, the next slide is one of the autopsy studies --

A Yes.

Q -- on autistic children, correct?

A Yes. This came out again this year, 2008, and it points out again that there's an increased density of glial cells for autistic children. There

is a decreased neuronal density, and then there are various signs of oxidative stress which can be shown by doing various tests. There were also differences in some glial cells.

As the Special Master said, you can go on to read this later. Next slide, please?

Q Well, let me stop you.

A Yes?

Q Go back to the bottom point here, Area 22. This paper was selecting areas of the brain that they suspected would be involved in some of the aspects of autism, right?

A Yes.

Q And in Area 22 what did they find?

A They found the greatest increase in glial cells, the greatest neuronal decrease and the greatest increase of nonspecific cells containing lipofuscin, which is an indication of oxidative stress.

Q What is lipofuscin?

A It's a complex I want to say fat protein. I don't remember exactly what it is, but I remember I have it in my notes.

Q Okay. We can ask Dr. Kinsbourne. And then briefly we refer to the Vargas paper, which I'm sure was discussed in Cedillo. That's another autopsy

study of autistic children.

A Yes. Their findings indicate that innate neuroimmune reactions play a pathogenic role in an undefined proportion of autistic patients.

Q Innate neuroimmune reactions. They're referring there to the glial cells, aren't they?

A Yes. Yes, they are.

Q In the brain?

A In the brain.

Q Okay. Now let's go to the next slide.

A This might be of interest to the Special Masters. It was certainly of interest to me. It doesn't have anything to do with autism, but it shows you what can happen with mercury and how it can surprise clinicians if clinicians keep their mind open and look for causes or differences in various pathological conditions.

They are studying idiopathic dilated cardiomyopathy, and they've studied the amount of mercury and other metals. In controls, the mercury was eight nanograms per gram. In people with this disorder there was 178,400 micrograms, so that's almost 20,000 times more in these IDCM.

So this indicates that mercury can concentrate in specific tissues or organs of the body,

even if mercury blood levels are found to be in the normal range. This is a very interesting paper because a lot of people missed it.

There's a tremendous amount of mercury. I mean, that's roughly 178 micrograms of mercury in this heart tissue that they found, and this will be of importance later on when we talk about mercury efflux disorders, but here is certainly a case where these people or this person -- I've forgotten what it was -- could not get mercury out of their heart cells. No question about it. One hundred and seventy-eight micrograms compared to a control of .008 micrograms.

Next slide, please?

Q Okay. Now, you refer to a mercury efflux disorder. What do you mean by a mercury efflux disorder?

A One cause of autism is the cells cannot efflux mercury. That is, there is no mechanism for getting mercury out of the cell. The normal mechanism by which mercury gets out of the cell usually is that it ties up the glutathione, and the glutathione mercury complex moves out of the cell.

Q All right.

A In the mercury efflux disorder, it implies that there's mercury in the cell and it can't get out

of the cell so the mercury concentrations in the cells increase.

I'd like to give the evidence for this. The next slide, please?

Q Now, you discussed Wilson's disease at some length in the Cedillo trial, didn't you, as an example?

A I don't remember, to be actually honest with you. I thought we did not, but I know we discussed it.

Q Well, quickly, Wilson's disease is an example of another metal efflux disorder, correct?

A Yes. I'll make it very short. In Wilson's disease, copper cannot leave certain cells, and the copper accumulates in the cells and it becomes very toxic to the cell.

Until John Walsh, a neurologist at Cambridge in England, thought about using chelating agent people with Wilson's disease would die very, very early in life, but because of John Walsh and other people subsequently who used the penicillamine and other chelating agents to get the copper out of their tissue, this at the time and still is one of the few genetic diseases that is treatable. These people now live to at least 40 or 45 years of age.

I wanted to tell you that there is another good example of an efflux disease, well documented in the literature, called Wilson's disease or hepatolenticular degeneration.

I think you can skip the next. Keep going. Okay.

MR. WILLIAMS: We've been going almost two hours here without a break.

SPECIAL MASTER HASTINGS: Do you want to take a break?

MR. WILLIAMS: Yes. I probably have about 20 more minutes, I think, 20 or 25 minutes to go.

SPECIAL MASTER HASTINGS: Okay. Let's take a 15 minute break. We'll be back at 4:00.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We're back on the record for the additional direct examination of Dr. Aposhian. Dr. Aposhian, you're still under oath.

Mr. Williams, please go ahead when you're ready.

BY MR. WILLIAMS:

Q While we're waiting for the slide man to get here, let me ask you. In this next section of your testimony we're going to cover some examples of ways

in which autistic children process mercury different than normal children, right?

A Yes.

Q Okay. And is that what you call your evidence for a mercury efflux disorder?

A Yes.

Q Okay. The first example is hair?

A Yes.

MR. WILLIAMS: The next slide, Scott?

THE WITNESS: Oh, here we are. This is a study done by Holmes, Blaxill and Haley. Haley is head of chemistry at University of Kentucky or was at the time the study was done.

Amy Holmes, a private practitioner who treated autistic children, and she knew the questions about mercury that were unanswered as far as autistic children, and she knew about mercury in hair, and she remembered that most parents keep the samples of first haircuts of the child, so she convinced them and control people to bring in the baby haircuts.

The next slide will show the results. The autistic group, and this is now Mercury Levels in First Baby Haircuts. The autistic group was 0.47. The control group was 3.63. Now, this study has been criticized because the control group, 3.63, is too

high as compared to the normal population.

One thing one must remember is to get controls for autistics is a very difficult job for all people interested in autism research. You can always get autistic kids, whether it's hair or some other way, but to try to get age matched and sex matched samples is extremely difficult. But even if we look, if we forget the 3.63 and say that what the normal population is is usually about 1.0, you still have twice as much mercury in the hair of controlled children.

In addition to this -- now, this was done to atomic absorption -- the next slide I think will show the results of the MIT group where they used neutron activation analysis, a different kind of technique for measuring hair mercury. This also is an abstract of a paper given at the American Nuclear Society.

Now, most societies peer review abstracts. Whether this was done here I don't know.

BY MR. WILLIAMS:

Q Well, let me just ask you though. We've got two studies on the hair of autistic children compared to controls. What did they find? Were they consistent with each other?

A Yes, they were consistent, both groups,

although the second one was a smaller sample. They both found that autistic children had less mercury in their hair than their control or so-called normal children.

Q And from a toxicology points of view, what's the significance of that difference?

A The significance is that there is less mercury in these cases in the blood and therefore probably more mercury in the cells; that the mercury cannot get out of the cells.

The work of James also shows that autistic children have glutathione concentrations in their blood, and this also means that there would be less glutathione in the cell to bring out the mercury.

Q Is this evidence that autistic children tend to retain mercury compared to controls?

A This is one kind of evidence that can be interpreted as meaning that autistic children have more mercury in their cells than nonautistic children.

Q Okay. Now, the next example you were going to talk about was the Ip and DeSoto study again. We've already talked about that.

A Yes. I just want to bring your attention to the last sentence. Let me just read it: Moreover, the hair sample analysis results offer some support

for the idea that persons with autism may be less efficient and more variable at eliminating mercury from the blood.

Q Okay. We had talked about Ip with respect to blood levels before. We're now talking about the Ip study on hair levels, right?

A Yes.

Q And it was also consistent with the Holmes and the MIT study. Okay.

And then there's another example of chelation therapy if we go to Slide 89.

A Yes.

Q Now, explain quickly what chelation is.

A Sure.

Q You've had some experience with chelation?

A Yes. Metals, as I've told you earlier, are bound to proteins and other substances in the body. They're not floating around free. So in order to get rid of metals you want to put something in the body that's going to have a greater affinity for that metal than the ligand or the protein that's holding onto the metal in the body.

And so by giving a chelating agent, if it's the right chelating agent it will have a greater affinity for that metal or the metal will have a

greater affinity for it than for the ligand or the protein to which it is attached in the body.

The term chelate comes from the Greek word chelos or claw, and essentially a chelating agent forms a five membered ring, a claw if you will, with the metal and makes that metal more water soluble. Since it becomes more water soluble it is excreted much more quickly and in larger amounts than if no chelating agent was given.

Q Okay. And this study by Bradstreet and others was a study of chelation in autistic children?

A Yes. What they did was give DMSA. We're involved in the FDA approval of this. DMSA was used originally. The FDA approval is for children with lead levels of 45 micrograms or greater per deciliter of blood, and DMSA is given to get the lead out of the body. It also can be used for off-label studies as we say because its safety has been proven. DMSA will also mobilize mercury and bring mercury out of the body in the same way.

What Bradstreet did was to give DMSA, this water soluble chelating agent, to autistic children and control children and, depending on which figure you look at or which table you look at, you find a very definite increase, anywhere from a three to

eightfold increase in mercury excretion when the autistic children were given DMSA chelating agent versus the control children. This is an indication that there was more mercury coming out.

Now, let me again say this study has also been criticized. All these studies have been criticized. There are very few studies in science that we cannot criticize. One of the exercises in most graduate schools is to give a student a paper and say we want you to report what's good and what's bad about this. These are peer reviewed studies.

You can always find something wrong with a study. This one has been criticized because they said the number of controls was too small. They also said there was bias in picking the controls, but the fact remains the paper appeared in a peer reviewed journal. The fact remains it's been reported many times, both personally at meetings and in the literature, that DMSA does increase the mercury excretion as compared to controls.

Q And is the result here consistent with the hair studies we talked about?

A Yes, it is. It's consistent with a greater body burden, a greater amount of mercury in the cells.

Q All right. Then let's skip to Slide 92,

please. What is this study?

A Okay. This is an unpublished study from our laboratory. We just haven't had time to publish it.

We have for most of the cases 16 autistic children with 22 controls about the same ages. For mercury in particular we had 14. There are some urines that just got lost in the shuffle, or there were some contaminated urines that were not used. For autistic children there are 14 for mercury studies. There are 14 children and 22 controls.

The equipment that we use, the latest equipment there is available, simultaneously determines within 10 minutes all of these metals on one urine sample, so we don't have all the manipulation errors that many people have that are doing atomic absorption where they do one metal at a time.

What we notice here is that the only significant difference between autistic children and control children is the mercury excretion. Here we have P less than 0.03. There's another slide which I forgot to bring with me that shows even a greater difference with mercury, but there certainly is less mercury coming out of children, autistic children, who are not given chelating agents than normal children.

Q So again is this consistent now with the hair study and the Ip blood study?

A It's what we would expect, yes. We were very excited to find this result. This has been presented at a number --

Q We have seen five or six studies --

A Pardon?

Q -- which show that autistic children seem to retain more mercury than nonautistic children.

A Yes. Yes.

Q Again, we talked about DeSoto, but there is one quote from DeSoto I think you wanted to show on Slide 93. Do you see the underlined part?

A Yes. In the DeSoto paper, just let me read the last part of it. Under Figure 1, they point out the variability found in circulating levels of mercury in hair, so kids are different. There's a wide spread.

Also, what is underlined. This is consistent with the idea that autism may be partly related to a lesser ability to rid the body of neurotoxins such as mercury, so again this fits.

If I can have the next slide, which I think is the baby teeth? Yes. No. This is another one.

Q Yes.

A This we've talked about already, I think.
Q We've talked about that one.
A Yes.
Q Let's go on to the next one.
A Yes. I think we skipped the baby teeth, which must have been two or three back there. Adams. Essentially this paper shows --
SPECIAL MASTER HASTINGS: Now what are you talking about, Doctor? Which slide?
THE WITNESS: Pardon?
SPECIAL MASTER HASTINGS: Which slide are we on, or what are you talking about?
THE WITNESS: We're now on Slide --
MR. WILLIAMS: This is Slide 95, Special Master.
THE WITNESS: Yes.
BY MR. WILLIAMS:
Q This slide is a study of the difference between boys and girls in the way they retain mercury?
A Yes. What they're measuring here is the amount of mercury excreted in the urine over a period of time with children.
The black spots, these children have amalgams in their mouth. The white spots or open circles, these children have composites used for

dental fillings rather than mercury.

Q The amalgams have mercury?

A The amalgams are mercury fillings.

Q And we know that mercury vapor comes off amalgams.

A It's well accepted even by the American Dental Association that mercury is emitted from these amalgams.

Q And does this study first show that both types of kids, boys and girls, if they had amalgams did they have more mercury coming out or less mercury?

A What it shows is if they had amalgams in both cases more mercury was being excreted than if they had composites, number one.

Q Okay.

A Number two, more importantly, if you look at the red arrows it shows that by the seventh year the boys are excreting less mercury than the girls are, which is an indication that the boys are retaining more mercury than the girls are.

That's what the interpretation of the authors is. Boys retain mercury more than girls by not excreting as much of the mercury.

Q Okay. Now, I think you're right that the slide about the tooth study somehow got dropped out of

here, but why don't you just briefly describe the tooth study to the Special Masters?

A The study by Adams. We know from the work of Needleman, who used baby teeth as an indicator of biomarker for lead, so Adams thought he would look at baby teeth to use as an indication of mercury.

The amount of mercury or metal in the teeth is a reflection of how much is in the body at one time or another. Adams found that the mercury in the teeth of autistic children was at least twice as much as the mercury in the teeth of nonautistic children, again indicating that these children, these autistic children, have more mercury in their tissues and in this case in their teeth, which are certainly considered to be a tissue or an organ.

SPECIAL MASTER HASTINGS: Just for the record, I think there's a Slide No. 90 that refers to Adams, as Special Master Campbell-Smith just pointed out to me.

MR. WILLIAMS: I knew it was in his report.

THE WITNESS: Can we go back, Scott, to 90?

SPECIAL MASTER HASTINGS: I think you just described it.

MR. WILLIAMS: Slide 90 does discuss the teeth though. You're right. Thank you for pointing

that out.

THE WITNESS: Because that study again has been criticized, the tooth study. As they say when you go to meetings, it hasn't been confirmed. That doesn't mean someone tried to confirm it. It means that no one tried to do the exact experiment.

In one of these studies we cite, the editor of that journal, the *Journal of Child Neurology*, made a big point of saying that people don't get glory by trying to repeat other people's studies, and the NIH, National Institutes Health, of our government does not give money to investigators to repeat other people's studies.

And so the idea that the Adams work should be minimized because it has not been repeated is just pure propaganda. It doesn't belong in scientific argument.

BY MR. WILLIAMS:

Q Okay. Now one more. Let's go to Slide 97, please. I'll ask this question. Have there been some studies that have now identified at least one genetic marker of susceptibility to this mercury efflux problem?

A Yes. Woods from Seattle and his associates have shown genetic polymorphism of the coproporphyrin

gene -- actually the oxidase gene -- and has shown that 15 percent of the population, of the dental population in this case, have a different reaction to mercury than do the rest of the dental population.

This finding represents the first report of a polymorphism. In other words, something has been changed in the gene that modifies the effect of mercury on a biological process, and they are now proposing that this be used for a biomarker of mercury exposure. It's a very readily testable phenomenon.

Q And is it your opinion that in the children that we've seen that have more mercury in their blood, less mercury in their hair, more mercury in their teeth, do they probably have genetic differences from the others too?

A I think there's no question. Most people would say they must have genetic differences to have those kinds of results.

Q Okay. Let's go to your second hypothesis quickly about Terbutaline. That's on Slide 98, if you would.

A Terbutaline is an example of a teratogen that can cause some types of autism via a neuroinflammation mechanism.

Q Okay.

A The next slide points out that Terbutaline has been a drug that has been used in the clinic to arrest preterm labor in women. We're not talking about animals now. We're talking about pregnant women.

It has been shown that the critical period corresponds to the second and third trimester in the human fetus. The human fetus is exposed to Terbutaline, and if there is a predisposition to having the damage there's a greater chance that the child will have autism. It causes decomposition of central nervous function like that reported in autism.

Q Okay. I showed in the opening statement an animal model of this Terbutaline toxicity, and Slide 101 I think has that paper on it.

A Yes.

Q If you would go to that?

A Yes. Results from animals can be used to trigger studies of human populations for exposure and outcomes, and there is a paper by Zeratte I think from the Hopkins group, if I remember correctly.

Results are overstimulation of the adenoreceptor during an early critical period. Results are microglial activation associated with innate neuroinflammatory pathways and behavioral

abnormalities similar to what is seen in autism.

Q When it says similar to what is seen in autism it's referring to those autopsy children of autistic children?

A Yes. Yes.

Q The Vargas paper and the Lopez-Hurtado paper and so forth?

A Yes. Yes, sir.

Q And then is this microglial activation the same thing that happened to the adult monkeys in the adult monkey study --

A Yes.

Q -- with the inorganic mercury in their brain?

A Yes. Inorganic mercury did cause that.

Q Okay. Let's go quickly to your summary slide on 106, please, and summarize your opinions here if you would.

A I don't think it's necessary to repeat the first one --

Q Okay.

A -- because we don't know about species of mercury, but I think it's necessary to speak about the Carvalho, et al. study, in particular the remarkable potency of the mercury compounds to bind the selenol-

thiols in the active site, and thioredoxin reductase should be a major molecular mechanism of mercury toxicity.

The first hypothesis: One cause of autism is that cells cannot efflux mercury, including thimerosal, and the DeSoto paper goes on to confirm that. That is a rebuttal of the Ip paper.

The second hypothesis: Terbutaline is an example of a teratogen that causes some type of autism via a neuroinflammation mechanism. Again, the Zeratte and other papers show that the behavior of abnormalities after Terbutaline are similar to autism.

In my opinion, based on 55 years' experience of being an independent biomedical research investigator funded by the federal government and private foundations, the first and second hypotheses are scientifically reasonable and probable.

Q Now let me ask you this question. Do you have an opinion as to whether or not injections of thimerosal in vaccines in human infants would deposit measurable amounts of inorganic mercury in the brains of those kids?

A What would happen would be the thimerosal would be broken down to ethyl mercury. The ethyl mercury would cross the blood-brain barrier, and in

the brain that ethyl mercury would be de-ethylated to give inorganic mercury or mercuric mercury which would stay in the brain.

Q Just as it did in the infant monkeys? Is that right?

A The infant monkey study, certainly a whole batch of them, including the most recent -- I think 2005 -- Burbacher paper.

Q And do you hold that opinion to a reasonable medical scientific probability?

A Yes, I do.

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

SPECIAL MASTER HASTINGS: All right. Do any of you have questions for Dr. Aposhian at this point?

SPECIAL MASTER VOWELL: Not at this point, no.

SPECIAL MASTER CAMPBELL-SMITH: Not at this point.

SPECIAL MASTER HASTINGS: All right. Let me ask one question, Dr. Aposhian, before we go on and see what the Respondent wants to do at this point.

Now, you filed an expert report with us back on August 30 of last year. I don't know if you recall preparing that.

THE WITNESS: I remember preparing it and having a very short period of time to prepare it because someone dropped out because of cancer.

SPECIAL MASTER HASTINGS: All right. A number of the articles that you talked about today were included in here?

THE WITNESS: Some of them were. Some of them of course have been published since then.

SPECIAL MASTER HASTINGS: Right. Of course, articles that have been published since you wrote this report couldn't very well be in this report. I understand that.

In general, did you put in all the articles that you at the time thought were important to the issue?

THE WITNESS: At that time I wrote that article I put in the papers that I thought at that time were important.

SPECIAL MASTER HASTINGS: All right.

THE WITNESS: I really haven't kept track, but it's sort of like preparing a lecture or at a symposia. You never finalize it until the minute before you walk in and give it, and so there are always changes to be made, especially over the last almost year. I'm sure there are papers.

If the question is are there papers here that are quoted that were not quoted in the initial report, the answer is yes.

SPECIAL MASTER HASTINGS: Tell me why. I mean, obviously aside from the obvious ones that were published since then.

THE WITNESS: Yes. Let's see. I don't know how to put this without making it personal.

I've had two members of my family seriously ill. When I was asked to participate in writing that report they were not ill. Shortly thereafter they became ill, and I had I think a month from the time that I think it was Dr. Lusier who dropped out because he had cancer, so I had a very limited time to prepare that report, whereas I had much more time to prepare this talk. Does that answer your question, sir?

SPECIAL MASTER VOWELL: Based on Special Master Hastings' questions, I have a couple follow-up questions, Dr. Aposhian.

Were you ever asked to prepare a supplemental report; that is, a rebuttal report?

THE WITNESS: I don't think so. I didn't see the Respondent's reports until maybe a month ago. I don't remember the exact timing, but I certainly was not asked to prepare a rebuttal, and there's nothing

in here that I can think of except -- well, actually the rebuttal about this poison determined the dose, if anything that was rebuttal to what was brought up in the Cedillo trial.

I must actually state that -- how should I put it -- I certainly would like more time to read the Respondent's reports. To my knowledge, I did not prepare any kind of rebuttal to the present Respondent's reports, to the best of my knowledge.

SPECIAL MASTER VOWELL: So you were not aware that there was a March deadline or early April deadline to file rebuttal reports?

THE WITNESS: I don't know. I honestly don't know. You can't imagine what it's like to have two people in your family seriously ill.

SPECIAL MASTER VOWELL: Oh, yes, I can, Dr. Aposhian.

THE WITNESS: Okay. We don't believe in health care providers. We think the family should take care of their own, and so I just don't remember the timing. I'm sorry. But I know no one asked me to prepare a rebuttal.

SPECIAL MASTER VOWELL: Well, let me phrase it this way then.

Your slides are dated 5-12-08 at least on

Petitioners' Trial Exhibit 2. Is that when these slides were prepared?

THE WITNESS: Excuse me?

SPECIAL MASTER VOWELL: These slides, Petitioners' --

THE WITNESS: Yes. These slides, they were prepared yesterday. Honestly.

When did I begin? This is May. I think I was told in April or the end of February when the date of this trial was set and so it would be my normal inclination in any talk that I was preparing to give anywhere that I would try to bring it up to date and try to improve to the best of my ability to give the best talk that was most relevant.

SPECIAL MASTER VOWELL: I have nothing further.

THE WITNESS: Have I done something wrong? I'm not sure.

SPECIAL MASTER HASTINGS: No. I think you've answered our questions.

THE WITNESS: Okay.

SPECIAL MASTER HASTINGS: Mr. Matanoski, how do you propose to proceed at this point?

Obviously Dr. Aposhian did cover some of the topics that were covered in his expert report and some

topics that weren't covered in his expert report. Do you want to cross him on the topics that he did cover? How do you propose that we proceed at this point?

MR. MATANOSKI: We have about two and a half hours of cross-examination based on his expert report. It seems that some of the testimony we didn't get today was matters that were in his expert report. I'm not sure how much of that --

SPECIAL MASTER HASTINGS: Do speak up.

MR. MATANOSKI: I'm sorry. I'm having the same problem with my voice that you are, sir.

I believe we probably would still be at about two and a half hours to cover some of the topics that he covered today which were covered in his expert report.

Then there are some new questions that have suggested themselves obviously based on things that he's covered today, although as I mentioned in our bench discussion they may be the subject of further proceedings or motions I should say after this trial or during this trial.

So we could go ahead and forge ahead with what we have, which would be about two and a half hours. We're prepared to do so, sir.

SPECIAL MASTER HASTINGS: Why don't we make

some use of our time? Why don't we begin your cross-examination?

MR. MATANOSKI: Very well, sir. Could we then have a brief break for Ms. Renzi, who will be doing it, to get her notes together? I mean brief, sir.

SPECIAL MASTER HASTINGS: All right. How much time do you need?

MR. MATANOSKI: Ten minutes, sir.

SPECIAL MASTER HASTINGS: All right.

MR. MATANOSKI: Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: Good afternoon again. Please be seated.

To those listening at home, we're again back for the last segment of our proceedings this afternoon. Dr. Aposhian is still on the witness stand.

Let me mention a couple things before we start with Ms. Renzi's questions here. First, that we thought it would be a good idea, given we have two witnesses scheduled for tomorrow, that we would get some of Dr. Aposhian's cross in today.

If you have a logical breaking point at some point before 6:00 I think we don't want to go past

6:00 today. If you have a logical breaking point at some point prior to that, Ms. Renzi, let us know. Maybe we'll stop at that point.

The other point being just to say for the record that as Mr. Matanoski mentioned earlier, we did have a conference at the bench earlier today. As he alluded to, at that point there was raised a motion that was filed in the King case and perhaps in the Mead case too, but it's relevant to both.

It was filed on Friday afternoon electronically having to do with a reference to a number of medical articles, over 200 medical articles, that were filed last week that were new to the case filed by the Petitioners, cited by them, that were not previously discussed in expert reports of either side and raising that issue, the issue of what to do about that and asking that the Petitioners be prevented from making reference to these articles in their own expert direct examination.

The representation had been last week at a status conference that the purpose of filing these articles was to make them available for cross-examination of the Respondent's experts.

Mr. Matanoski did mention that some of those articles had been raised today in the examination of

Dr. Aposhian and perhaps in Dr. Greenland as well, in the direct examination of him, and that the government was considering filing an additional motion seeking additional relief here.

Again, we note that we will hear that motion whenever you want to present it, or you can file it in writing. We'll wait to hear exactly what you have in mind, but obviously a couple of our questions to Dr. Aposhian were addressed to that issue. We'll wait for what the government proposes to do about that issue explicitly at this point.

What that, Ms. Renzi, whatever questions you had for Dr. Aposhian this afternoon, go ahead and go for it at this point.

MS. RENZI: Thank you, Special Master.

CROSS-EXAMINATION

BY MS. RENZI:

Q Good afternoon.

A Good afternoon.

Q Dr. Aposhian, you said you were currently a professor at the University of Arizona?

A I'm professor emeritus. I retired on January 31 to take care of my wife and other people in my family, but I still have an active laboratory with funding for research for two more years.

Q Do you know if you're listed on the University of Arizona website as a faculty member or a professor emeritus?

A Excuse me?

Q Do you know if you're listed on the University of Arizona website as either a member of faculty or as a --

A I don't have the faintest idea. I don't read that sort of stuff, but I do have letters that I can send you from the president of the university and from the medical school people saying that I have emeritus status. I would never dare say anything that was not so.

Q Okay. Are you listed as a professor at the Pharmacology School of Medicine? Do you know that? Do you have emeritus status there as well?

A For the last 32 years I've been listed in the catalog of the medical school as Professor of Pharmacology.

Q Do you know Glen Sipes, the chair of the Pharmacology Department at the University of Arizona?

A Excuse me?

Q Glen Sipes. Do you know Glen Sipes?

A Yes. I know Glen Sipes very well.

Q Is he a well-respected toxicologist?

A Of course he's a well-respected toxicologist.

Q And do you know a man, John Sullivan, at the University of Arizona?

A I don't know him personally. I know of his reputation. He's a very good clinical toxicologist.

Some people use the term medical toxicologist, but I think the board, and again you can correct me. I think the board uses the term clinical toxicologist.

DR. JEFFREY BRENT (From the gallery): The board uses the term medical toxicologist.

THE WITNESS: It changed then. Okay. Because two of the members at the University of Colorado spent time in my laboratory, and one of them took time off to study for her board exams in clinical toxicology.

BY MS. RENZI:

Q Now, you're not a medical doctor. Is that correct?

A That's absolutely correct.

Q And you're not a medical toxicologist. Is that correct?

A It depends on how you define the term medical toxicologist. I was brought in by the Chinese

Government. I was brought in by the Chilean Government. I was brought in by the Inner Mongolian Government as a pro bono consultant to deal with a population of people who were drinking water with elevated levels of arsenic.

Q But you don't have --

A Excuse me. Let me continue.

Q Okay.

A And so I took a team with me, and I was the person responsible for everything. I was the person that wrote up the reports. I dealt with humans.

Now, am I a medical toxicologist? I don't like the term. I'm a toxicologist.

Q But you don't have a medical degree to be called a medical toxicologist?

A I have no medical degrees, as I've told you before.

Q That means you're also not a neurologist. I that correct?

A Pardon me?

Q You're not a neurologist?

A Obviously I can't be a neurologist when I don't have an M.D.

Q Do you consider yourself qualified to comment on the neurological aspects of autism?

A It all depends on what parts of the neurological aspects you're talking about, but I would certainly take second place. I would prefer that a medical neurologist answer such questions.

Q Are you an immunologist?

A I'm not an immunologist.

Q Do you consider yourself qualified to opine on the immunology as it relates to autism?

A Again, it depends at what level you're speaking of. If you want me to go into the very fine levels of immunology as far as applying to humans, I would certainly not want to speak that way.

I am a basic science bench investigator. I work at the lab bench, and I go study populations of people at the invitation of governments throughout the world.

Q Have you ever published a peer reviewed article on mercury in the immune system?

A No, I have not.

Q Have you ever published a peer reviewed article on autism?

A We are now in the process of writing a review article that we've been asked to write by an international journal as a toxicologist's view of autism. I expect the article will be finished

sometime this summer.

That was an invitation for the article. We did not ask to do it. They invited us to do it. An invitation.

Q Have you ever published a peer reviewed article on thimerosal toxicity?

A I don't remember whether some of our abstracts -- I would say no.

Q Have you ever published a peer reviewed article on ethyl mercury toxicity?

A On what?

Q Ethyl mercury toxicity.

A Not published, but we've given many talks at symposium. The Institute of Medicine invited me. I actually did not want to go.

They invited me in I think in was 2004 I think it was to speak at one of their vaccine committee meetings on "A Toxicologist's View of Autism and Thimerosal".

Q Do you consider yourself an expert in autism?

A I consider myself an expert on the relationship of mercury to autism.

Q And when did you acquire that expertise?

A When?

Q Yes.

A Let me tell you the story. In I forget whether it was 2002 or 2003 I had a call from the administrative assistant to Congressman Burton of the House Government Oversight & Regulation Committee. I think it's called that.

At that time the administrative assistant -- she actually -- asked me whether I would come and talk to the committee on mercury toxicity. I said certainly, but why are you interested in mercury toxicity? This was probably five years ago I would say. They said we're really interested in autism, and there's mercury involved. I said okay.

I went home and decided I really didn't know what autism was. I have two daughters who have PhDs in clinical psychology. I called them and I said what is autism? They in fact were delighted to know something that their father did not know and so I first learned about autism at that time.

Since then there have been many organizations like the Institutes of Medicine and other organizations that wanted someone who had more or less a fresh view of autism that was not part of any establishment as far as autism is concerned and so in the last five years I've become very interested in

autism.

Q Are you aware of the Diagnostic and Statistical Manual of Mental Disorders, otherwise known as the DSM-IV?

A I'm aware of it.

Q What are the criterion for an autism diagnosis?

A I would certainly open up the book and read them.

Q You don't know them?

A There are regulations that I don't know. That's some of them. I can talk about other regulations I don't know either. If it's something that you can find on the web or in a book there's no sense of memorizing, especially since you don't use it every day.

What we were concerned about was all our autistic subjects in our urine studies were classified by a physician by the usual standards that you've just mentioned and the other standards for autism.

Q You've published several articles on chelation. Is that correct?

A I would say many people think my major contributions since 1979 have dealt with chelation.

Q Would you agree that you're not qualified to

diagnose or treat a person with ethyl mercury toxicity?

A I have never claimed I have been.

Q Would you agree that you're not qualified to diagnose or treat a person with any form of mercury toxicity?

A It all depends now on how you want to define diagnosis. Very often a physician will call me and say Vas, we have this case here and the urine mercuries are this much. The blood mercuries are such and such. We've done a biopsy, as the case just happened now, of someone's gut and we want to know whether you think it's worth doing a mercury analysis or you think this person may have mercury toxicity.

What I usually say, as they well know, is John, Joe, whatever your name is, I'm not a physician, as you know, but based on what you've told me it seems to me that that person is mercury toxic.

But would I stand up in a Court of law and say hey, I'm an expert in diagnosing humans? No, I would not because if you're going to deal with humans on a diagnostic and treatment basis -- not a research basis, but a diagnostic and treatment basis -- then you should be an M.D.

Q I want to move on to dose. You quoted today

from Casarett & Doull, the book on toxicology, correct?

A Yes.

Q Would you agree with the statement that's in that book that no other metal better illustrates the diversity of effects caused by different chemical species than does mercury?

A Are you asking me whether I agree with this?

Q Yes.

A I have no disagreement with it.

Q Would you agree that different species of mercury have different toxicological properties?

A I'm sorry? I didn't hear you.

Q Do different species of mercury have different toxicological properties?

A That was I think quite apparent from the talk I gave or my testimony earlier.

Q Could you please define dose for me? What is dose?

A Dose means different things to different people. If you're a scientist and are concerned about dose then you'll want a quantitative value that tells you how much you are giving to a certain animal or human being.

You want a quantitative value, and that

quantitative value could be milligrams or grams. It could be milligrams per kilogram. It depends on who is prescribing, and I don't prescribe to humans, of course.

Q Would you agree that any substance could be toxic to humans based upon a dose?

A The point I have tried to make in the testimony is that dose is not the only criterion for toxicity; that many other criterion come into play when you discuss toxicity, and that was shown in at least two or three of my slides from the textbook that you have just quoted.

Q What is the principle of dose response?

A Dose response usually means -- not all the time -- that as you increase the dose you increase the response, or as you decrease the dose you decrease the response usually in a fairly straight line, but, as we know, especially in the case of arsenic toxicity that when you get down at lower levels it goes off the straight line.

Q Is it still your opinion that the principle that dose makes the poison is no longer accepted by the general toxicological community?

A That's not what I said. It is one of the factors that determines toxicity, but it is not for

anyone to get up and say dose determines the poison. It's a very limited way of looking at toxicology, a very limited way of looking at a poison.

There are many factors in that very chapter that you quoted with Goyer which I presented earlier and you have copies of various other things that affect the toxicity. It's not only dose that affects toxicity.

Q So that principle is no longer accepted by the general toxicological community? Is that what you're saying?

A I don't consider it a principle. It's something that man in 1400 or 1500 said, and anyone who thinks that toxicology has not progressed enough to change and have a different view about someone's statement in the year 1490 or whatever it is I think has a very limited outlook on medicine and science.

Most of the people that I know, Sipes included, would say dose is one of the factors that determines toxicity or determines poison. It's not the only factor.

Q Would you agree that in toxicology a threshold dose is expected before a particular outcome is observed?

A Before?

Q That you would have a threshold dose before a particular outcome is observed?

A I don't know what kind of generalization you're trying to make. I certainly know that response is related to dose, but dose is not the only thing that determines response. Is that clear?

Q We'll move on. How much ethyl mercury is there in a thimerosal-containing vaccine? How much ethyl mercury is there in a thimerosal-containing vaccine?

A It depends on which vaccine it is. I think in one case -- I can't remember which vaccine -- it's 12.5 micrograms if I remember correctly. In the other case of a vaccine it's 25 micrograms.

Q And I know you had this on your slide presentation earlier. How many micrograms are there in a milligram?

A There are a million micrograms in a -- I'm sorry. There are 1,000 micrograms in a milligram. Isn't that what it said?

Q Yes.

A Okay. Thank you.

Q And how many micrograms are there in a gram?

A There should be a million micrograms in a gram.

Q Dr. Aposhian, is it scientifically valid to compare the doses of ethyl mercury that are in a thimerosal-containing vaccine, and I'll use TCV from now on if that's okay.

In a TCV, is it right to compare those doses --

A I don't like the term TCV. I don't like abbreviations. Would you mind saying the whole thing? We have computers now that can print things up very carefully, and I think it's much clearer if we don't use abbreviations, if you don't mind.

Q If you would like me to say it, that would be fine.

A Thank you. I appreciate that very much.

Q I'll repeat the question then. Is it scientifically valid to compare doses of ethyl mercury that are contained in a thimerosal-containing vaccine to the exposures of methyl mercury that occurred in Iraq and Minamata?

A It all depends on what you mean by compare. If you're saying do you want to see if each of them is toxic, yes. If you want to say is one more toxic than the other, I'm not sure you can do that, so I'd like to ask that you ask me if possible a more specific question.

Q Can you compare the 12.5 micrograms that are contained in a thimerosal-containing vaccine to the doses that were exposed to the people who ate the grain in Iraq and who consumed the fish in Minamata?

A No question about it. I now understand your question. I'm sorry. I didn't mean to interrupt you.

Q Okay.

A My apologies.

Q No. That's my question.

A Okay. There is no comparison. The amount that was used, the exposure in Iraq was much, much higher.

We were talking in the talk I gave earlier in I think it's the Rooney paper explained the differences between a chronic high dose and a chronic low dose. Certainly if you want to talk about chronic doses the exposure of children getting vaccines would be considered to be a chronic low dose whereas the Iraqi people being exposed to the various forms of mercury in the flour that the U.S. Government gave them, that would be considered a chronic high dose.

Q Do you agree that the researchers in Iraq and Minamata established a dose/response relationship in their studies?

A I've got to be very careful here because the

Minamata studies are so old. My guess is yes, they did, but I just don't remember the particular paper with the particular dosage, but I'm sure Tom Clarkson, knowing how he works, did establish. I would suspect that Tom Clarkson did establish a dose/response curve in Iraq.

Q Have you read the 1973 Bakir article, B-A-K-I-R?

A Which one? I've read all the Iraqi articles, and some of the names I have difficulty remembering.

Was that the one? There was one -- I'm not sure whether Clarkson was the first author or he was -- which showed that depenicillamine was one of the best ways of getting rid of mercury in the blood. Is that the article you're talking about?

Q I'm talking about an article that was filed on Petitioners' Master List 178. We can hand you that article if you'd like to see it.

A Yes, I would like to see that article, please.

(Pause.)

A This is a very old article. I'm not sure I remember reading everything about it, but I do remember that when it came out I read it and maybe a

couple times since then, but not recently.

What would you like me to address in this article?

Q Do you recall the threshold dose of mercury that was observed in Iraq before effects of toxicity were observed?

A I don't recall at all.

Q I want to refer you then to page 238 of that article.

A Page 238.

Q Okay. I think it's the top center column. We have it up on the screen as well.

A Excuse me. You're talking about Figure 7?

Q I'm talking about the paragraph that's highlighted. It should be on your screen, sir.

A Oh, I'm sorry.

Q It says: Nevertheless, the threshold value of 25 to 40 milligrams of mercury as computed for parasthesis agree remarkably well with the threshold figure of 30 milligrams of mercury computed by the Swedish expert committee from data on the Japanese epidemics.

Would you agree then from that article that there was a threshold value of 25 milligrams of methyl mercury?

A I agree that nevertheless, the threshold value of 25 milligrams of mercury was computed for parasthesia agrees remarkably well with the figure of 30. Is that what you're asking me?

Q Yes.

A I have no argument.

Q Now, the threshold value of 25 milligrams.

A Yes?

Q What is that equal to in micrograms?

A Twenty-five milligrams would be 25,000 micrograms.

Q In either one of those epidemics, either in Minamata or in Iraq, was there an increase of autism reported as an outcome of the affected populations?

A No one even thought of autism in those days. You should ask Tom Clarkson, who is a fantastically good scientist. People have asked him that, and his response is no one thought about autism in those days.

I think most people did not know what autism is. I think most medical students were not taught anything about autism, so it's not surprising that no autism cases turned up.

Q Do you know if the clinical effects then that were reported in either the Iraq or Minamata study resembled autism? Even if we didn't know what

autism was, were any of the elicited effects clinically significant for the diagnosis of autism?

A Well, as I remember, and again it's been a long time since I looked at these studies, but as I remember there were cerebral palsy like effects that they found. You've read the article more recently than I have.

There was certainly without any question central nervous effects on young children and children that were born.

Q Do these clinical effects resemble autism?

A Since I wasn't there and did not examine the children or wasn't there when a physician examined them, I just don't feel comfortable answering that question one way or the other. I would be guessing at it.

Q Could you clarify your opinion as it relates to the thimerosal-containing vaccines we're discussing today? Does dose matter in these cases whether thimerosal-containing vaccines cause autism?

A Certainly when you consider that a child over a short period of time relatively, it's possible for him or her to get 187 micrograms of mercury.

That's a large dose for a child who has a very low body weight so on a per kilogram basis my

scientific assumption, based on the data I have so far, would be that those amounts of thimerosal could cause autism in some children.

Q Do you have to get the entire 87.5 (sic)?

A Pardon?

Q Do you have to get the entire series of shots, the 187.5 micrograms?

A I don't know that. Again, it depends upon the susceptibility of the child and the metabolism of the child as to how he or she handles that mercury.

When you talk about dose determines the poison as some other people would say, you could also have a child with a small dose or the large dose having the same effect.

Q So let's assume that your hypothesis that we have a genetically susceptible child is true. Could 12.5 micrograms cause that child to have autism?

A If we knew that we would be able to do something, but that specific question in a specific child we don't know the answer to. All we know is there appears to be a relationship between the amount of mercury that children are exposed to via the vaccinations and whether they get autism or not.

You heard what was said this morning by the epidemiologist who quite honestly and carefully

debunked many of the epidemiology studies that have been published in the past. It was such a good rendition that I asked him to write a paper just on what he said.

Q But you don't know the dose it would require?

A Pardon?

Q You don't know the dose of ethyl mercury it would require for a child to have autism?

A No. I don't think anyone does because each child also would be quite different in his response or her response and there's tremendous variation.

MS. RENZI: I'll just have 10 more minutes of questions. Would that be okay?

SPECIAL MASTER HASTINGS: All right.

BY MS. RENZI:

Q Dr. Aposhian, you did not speak about this today, but it is contained in your report, and I would like to discuss some of the aspects of your report.

A Which? Today's report?

Q The report that you filed for the Court --

A Yes.

Q -- that we believed was going to be your testimony today.

A Do you think I could have a copy?

Q Sure.

A Thank you. Thank you very much.

SPECIAL MASTER HASTINGS: For the record, that's Exhibit 25, I believe.

MS. RENZI: I think it's Exhibit 19.

SPECIAL MASTER HASTINGS: Dr. Aposhian's report? Okay. Exhibit 19.

BY MS. RENZI:

Q Dr. Aposhian, on pages 6 and 7 of your report you discuss four factors that you believe can cause someone to be more susceptible to mercury. Do you have that?

A I have the page. Beginning on page 6, No. I, at the bottom.

Q Do you mean when you say susceptible to mercury, mercury toxicity?

A Pardon?

Q When you say susceptible to mercury do you mean mercury toxicity?

A I'm sorry. I can't understand you.

Q What do you mean by susceptible to mercury?

A I don't see the word susceptible at all on this page, on page 6. I've looked for it. In the bottom part that's typed I don't see the word susceptible at all.

Q Okay. We'll call them then factors of vulnerability.

A Where are we?

Q We won't say susceptibility.

A Where are you?

Q I'm on page 6.

A All right. Many other factors are involved in the vulnerability.

Q Okay. I apologize. It was vulnerability. not susceptibility.

A Your apology is accepted.

Q The first of these four factors of vulnerability that you say --

A Could you speak into the microphone? Thank you.

Q The first factor that you say increases someone's vulnerability to mercury. Actually, let's go back. Could you define vulnerability to mercury? What do you mean by that?

A You're asking me to define the word vulnerability? Is that correct?

Q Vulnerability to mercury.

A Yes.

Q The phrase that you used. Do you mean mercury toxicity? What do you mean?

A I mean their response to mercury. Their vulnerability to mercury would be their response to mercury.

Q And what would the response to mercury be? Would it be a toxic response?

A There's wide variation. In some people there would be high levels of mercury in the blood or high levels of mercury in the urine or high levels of mercury in the hair, or some people would have, depending on which species, a tremor.

There are all sorts of signs of the vulnerability of an individual to mercury, depending on what the species of mercury is also.

Q Okay. The first factor you say increases one's vulnerability to mercury is antibiotics, and that's on page 6 of your report.

A Yes. Antibiotics being used when mercury exposure occurs can inhibit mercury excretion and then potentially increases toxicity.

Q And you're referring to the Roland study? Is that correct?

A I'm really referring to -- I should have put this down -- Ann Summers at I think it's either the University of Georgia or Georgia State. I don't remember. She went there from Mass General where she

had a very distinguished career.

She has published many papers that show that not only exposure to mercury, but the number of amalgams in your mouth, can affect the amount of mercury that -- I'm sorry. The antibiotics can affect the amount of mercury you're excreting.

I think that's in good peer reviewed journals. I want to say proceedings in the National Academy of Science, but I'm not even sure which journal.

Q But that's not what you relied on in your report for this?

A Again, I'm sorry to bring up a personal matter. This report was written at a time in my life where I could not spend as much time as I usually do.

This report was written between 4 a.m. and 6 a.m. every morning and so there are shortcomings. I take that responsibility and I apologize to the Court for it.

Q Can I just ask you a question? Is the Roland study that you rely on no longer valid? Is that what you're saying?

A No, I'm not saying that. I'm saying that there have been more studies since Roland, namely Ann Summers and probably also Fritz Lorscheider. There

have been other studies that have proven the same thing; that antibiotics will decrease the excretion of mercury.

Q And you said with dental amalgams?

A Pardon?

Q With dental amalgams?

A With or without dental amalgams. Wherever the mercury comes from. In many experimental systems they expose them to mercury vapor, and there have been human studies I believe that show the same thing.

Q Now, the Roland study was a rat study. Is that correct? A rodent study?

A I don't remember the Roland study now. I would suspect it was a rat study, but I'm not positive.

Q You don't know the doses of methyl mercury that were administered?

A Definitely not. It's things like that you can look up and read in the paper. I don't believe in memorizing things like that.

Q We can hand you the paper.

A Sure.

Q Because I do have some questions on that.

A Sure.

(Pause.)

A Thank you. Do you want this one back, or should I keep this one? Thank you.

Now, we're looking on The Effects of Diet on Mercury Metabolism and Excretion of Mice Given Methyl Mercury, so it's mice and not rats.

Q Okay. Mice.

A Thank you for bringing that to my attention.

Q On the top of page 402 --

A Page 402.

Q And we can highlight that. We can put it right up on the screen for you.

A I'm on 402, but I don't know what you just said. I'm on page 402.

SPECIAL MASTER HASTINGS: Doctor, she has it on the screen.

THE WITNESS: Oh, I'm sorry.

SPECIAL MASTER HASTINGS: That may be easier for you.

THE WITNESS: Much easier. Thank you.

BY MS. RENZI:

Q Would you agree that the dose was .6 milligrams of mercury per kilogram?

A All right.

Q And wouldn't the dose of mercury be equivalent to 600 micrograms per kilogram of body

weight?

A Six hundred micrograms of mercury per kilogram of body weight. Is that what you asked? Yes.

Q And that 600 micrograms per kilogram of body weight would be equal to a 6,000 microgram dose in a 10 kilogram child. Is that correct?

A Well, they're talking about mice here. I'm not certain that you can just transpose a mouse dose to a human dose that quickly just by changing the weight, so I don't know what your point is.

Q My point is the doses are not comparable. Are those doses comparable to the amount of ethyl mercury contained in a thimerosal-containing vaccine?

A I don't claim the doses are comparable. I don't claim that's so.

Q But you said in your report that based on the Roland paper high doses of methyl mercury in mice inhibit the excretion.

A What page are we on now?

Q I'm sorry. You said that based on the Roland study that high doses of antibiotics --

A What I say, if you're talking about page 6, let's quote it correctly. Antibiotics being used when mercury exposure occurs can inhibit mercury excretion

and thus potentially increase its toxicity.

Q Right. But even with the administration of antibiotics, weren't the doses administered to the mice in this study much larger than the doses that are contained --

A I make no claim about dosage in this. All I'm saying -- and I quote the Roland paper here, whatever doses they're uses. That antibiotics being used when mercury exposure occurs can inhibit mercury excretion and thus potentially increase its toxicity.

Q So this study has no applicability to what antibiotics can do to a person who's exposed to thimerosal through a thimerosal-containing vaccine?

A I think what you've got to understand is science changes. Sometimes it changes the way you want it to change, whether it's you or me, and sometimes it changes a different way. In this case these studies showed that mercury excretion was inhibited by giving an antibiotic.

Now, I'm on very weak ground with the following statement, all right? I wish I had known you would ask this. I would have been certain. There may even be some --

Q It was in your report.

A Pardon?

Q It was in your report.

A No, no. Whether it's in my report or not doesn't matter. I just didn't realize I had to be prepared for this.

What I'm trying to say is there may be a study in humans by Ann Summers -- in fact, I'll make a point of calling her tomorrow. Either Ann or someone else did some studies I think showing that when humans were given antibiotics that there was a decrease in mercury excretion. That statement is usually accepted by most toxicologists today.

Q Of methyl mercury or ethyl mercury?

A I'm just talking about whatever mercury they were using at the time. I don't remember. I'm certain they didn't give methyl mercury to humans in experimental situations to prove that.

My guess is they gave it to probably humans that were ill. They gave them an antibiotic, and they also did a fecal excretion and a urinary excretion of mercury -- that's what my guess is -- and probably related it to their mercury exposure. I'm not positive of that, but that's what comes up in the back of my mind.

Q So you're not sure?

A I'm not sure. I'm telling you the truth

when I say I'm not certain.

Q Now the second factor you list on page 6 of your report. The second factor.

A Yes?

Q You state a factor may increase one's vulnerability. One factor is a combination of genetic predisposition and a stress such as fever may increase the impact of the stress causing agent, and you cite Morton.

A And what's your question?

Q The Morton article is entitled The Genetic Epidemiology of Hearing Impairment. We can hand you that article if you would like to see it.

A You brought up a very good point. I'll go back and see what the story is. It seems ridiculous for me -- no abstract available. It's also possible I have that in my library at home.

Q We have that article.

A I can't answer any more.

Q We have that article. I have it.

A Oh, is it in there? Can I see that? Thank you. Is it mentioned? I'll take your word for it. Is it mentioned?

Q Well, my question to you is you mentioned the article in your report.

A Yes, but what I'm asking you is do they mention stress and mercury in this report?

Q They make no reference to mercury.

A Then my guess is that it was a mistake and it should have been the Mutter paper immediately thereafter because the Mutter paper comments on the article, The Toxicology of Mercury and its Chemical Compounds, or another.

I don't know. You have a good point. I concede that point to you.

Q So can you cite to a peer reviewed article on the combination of genetic susceptibility and a stress with regards to thimerosal in autism? So a genetic susceptibility, stress, thimerosal leading to autism? Is that the article you did not --

A You're talking about No. 3? Is that what you're talking about?

Q Right. Can you cite to a peer reviewed article about a combination of genetic susceptibility and stress with regard to thimerosal and autism?

A Now, what is your question?

Q Can you cite to a peer reviewed article? You said that Morton doesn't apply in this case, correct?

SPECIAL MASTER HASTINGS: Doctor, she's

still on Point 2 at the bottom of page 6.

THE WITNESS: I'm at that point, and I don't understand what your question is. I can read the --

BY MS. RENZI:

Q Okay. If the Morton article doesn't apply, which you just said the Morton article should not have been cited, correct?

A You're absolutely correct.

Q Okay.

A I'm certainly not perfect.

Q Okay. Can you cite though to a peer reviewed paper that discusses the combination of genetic susceptibility and stress with regard to thimerosal causing autism?

A I'm not certain. Let me just check one thing. All these points refer not to autism, but they refer to the once accepted toxicology axiom that dose determines the poison.

Nowhere in that first paragraph on page 6 or on the second or under (1) or (2) do I see the word thimerosal or autism, so I don't understand what the point is, ma'am. I don't mean to be rude. I just don't understand.

Q Sir, you put these in your report about what makes people more vulnerable to mercury, and I just

want to go over this for the basis --

A But I don't say anything about thimerosal, and I don't say anything about autism here.

Q So these don't apply to thimerosal-containing vaccines?

A I don't know that. I'd have to think more about that. I think that these are generally accepted beliefs about the vulnerability of people to mercury. Antibiotics are generally now considered to inhibit mercury excretion.

Certainly many people accept the idea that there's a genetic predisposition to mercury toxicity, I think the effects of mercury, and there are a number of papers that prove that now.

I haven't said anything about thimerosal and autism in these lines that you're quoting.

Q The Palmer study.

A Okay. Let's go to the Palmer study. This study has been criticized probably quite well since this paper was published.

I'm not even sure. Again, it's been a long time. I'm not even sure they measured the mercury in the air. I just don't remember this paper well enough. If you have that paper I'd love to have it.

Q Why did you cite the Palmer study?

A Pardon?

Q Why did you cite the Palmer study?

A The Palmer study was cited because, as it says here someplace: The association between an environmentally related mercury, special education and autism rates in Texas was investigated using data from the Texas Education Department and the United States EPA.

There was a significant increase in the rates of special education students and autism rates associated with increases in environmentally released mercury. On the average, for each 1,000 pounds of environmentally released mercury there was a 43 percent increase in the rate of special education services and a 61 percent increase in the rate of autism.

Now, this study has been criticized, and just again it's been so long since I read this article. I don't remember all the criticisms, but the study has been criticized I think for -- I don't remember whether they themselves did the mercury determinations or if any mercury determinations were actually done.

Q Doctor, is it your opinion that mercury in the air causes autism?

A No, but that's not the only exposure that a person may have or a child may have or a mother, a pregnant woman, may have for mercury. It's not just mercury in the air.

I think in my slides today I made it very clear that exposure of humans to mercury in the air is not very important.

Q The fourth factor that you list in your report --

A Let me check the reference first to be certain it's correct. Yes.

Q Okay.

A This is an excellent book from the new Norberg group. Yes.

Q But the fourth factor you say plays a role in someone's vulnerability to poisons is diet. Is that correct? That's on page 7 of your report.

A Yes, one of the points.

Q And you state in your report that glutamine is low in autistic children. Is that correct?

A I guess that's what I say.

Q What studies do you rely on for the proposition that glutamine levels are lower in autistic children?

A I would suggest -- it's not a very good

reference -- that the new Norberg text, which is an excellent text that I recommend to anyone who's interested in metals.

It was just published in 2007, and there are chapters in there about glutamine, metals and autistic children, as I remember. It's a chapter in the Norberg book. I did not realize before that I did not put the page number down.

Q You state on page 7 in your report that glutamine is a precursor of glutathione.

A Glutathione is glutamyl, cysteinyl and I've forgotten the other amino acid, but glutamic acid certainly is part of glutathione.

Q Is it a direct precursor?

A Pardon?

Q It's not a direct precursor as you state in your report, is it, sir?

A In order to make glutathione, you have to have glutamyl cysteine is one of the precursors. In order to make glutamyl cysteine, you have to have glutamic acid.

Q What's the basis for your opinion on that?

A Pardon?

Q What is the basis for that?

A Go to any basic biochemistry textbook.

Q Well, we're going to pull up the Jill James paper, and that's Jill James 205. It's Petitioners' Master List 7.

We'll see from the homocysteine down to the glutathione. I don't see glutamine on there. Is glutamine a precursor to glutathione?

A But this is not the only way of making glutathione in the cell. If you look at the structure -- you must have someplace the structure, the chemical formula for glutathione. You'll see glutamyl, cysteinyl, glycine. I think that's what it is. Here we have cystathiomine. We have the cysteine. Let's see.

There are other pathways. This is not the only pathway for making glutathione. If you go to an elementary textbook of medical biochemistry you'll find three or four different pathways.

Q Assuming glutamine levels are low, are glutamine concentrations rate limiting in glutathione synthesis?

A I don't know.

Q So the concentration in glutamine doesn't determine the synthesis of glutathione? You don't know?

A I don't know.

Q How much lower are the levels of glutathione in autistic children compared to nonautistic children?

A Say that again.

Q How much lower are the levels of glutathione in autistic children compared to nonautistic children?

A You have a copy of the Jill James paper. It's in there.

Q You don't know off the top of your head? No? Okay. That's fine.

A The Jill James paper published probably last year or the year before.

Q Do you know how low levels of glutathione or glutamine have to be in order to inhibit the excretion of 25 micrograms of ethyl mercury?

A I have no idea. I have no idea.

Q Does the body have mechanisms other than glutathione to bind to, transport and eliminate ethyl mercury?

A If you read Clarkson's articles, which are good review articles on the whole, I think you'll see that the glutathione is considered to be the major pathway.

Certainly to get mercury, methyl mercury included, into the bile and into the feces it usually is combined with glutathione as one of the carrier

mechanisms. It may also be combined with glutathione tied up with other proteins, but they don't know that yet.

Q But there are other mechanisms? Is that correct?

A There are other mechanisms.

Q Could you list some of those mechanisms?

A Excuse me?

Q Could you list a few of the mechanisms?

A No.

Q I'll list some, and if you could tell me if I'm correct?

A Pardon?

Q Would selenium be one thing in the body --

A What about selenium?

Q -- that would help transport, eliminate and bind to heavy metals such as ethyl mercury?

A Now you're getting into a very difficult area because you're going to ask a specific question, so let me ask a specific question if I may that maybe you'd like.

Does selenium have anything to do with the excretion of mercury? Off the top of my head I would say no. Does selenium have anything to do with the detoxification of mercury? If you believe most of the

people who dabble in this sort of thing, they will say that mercury is very reactive with selenium, and a mercury selenide is formed, as I think I mentioned in my testimony.

This mercury selenium or mercury selenide is very, very insoluble. I doubt very much. I don't know what the data is, but I doubt very much that mercury selenide comes out in the body as such because it is so insoluble.

Does that answer your question at all? I don't want to make things difficult, I assure you.

Q That answers my question. I have another question for you.

A All right.

Q Is metallothionein something in the body that binds, transports and eliminates heavy metals such as ethyl mercury?

A Let's first deal with simple mercuric ions, all right? There's no question that mercuric ions have an affinity for metallothionein. Metallothionein is a protein of which I think one-third of the amino acids are cysteines, CYSH, free sulphydryl groups.

Metallothionein is used in the body as a mechanism, number one, for inactivating cadmium. Another metal may be lead and mercuric mercury is one

of them. I think methyl mercury forms a different complex with metallothionein, and I'm not certain what people feel is the significance of that as far as the excretion.

Certainly metallothionein is known to transport certain metals from the liver to the kidney, but whether it does that with mercury I don't remember. It is not considered to be a major pathway.

Q I want to move back to glutathione. Does glutathione protect against mercury? Does glutathione only protect against mercury, or does it protect and aid in detoxifying other substances?

A The concentration of glutathione in your liver cells is 10 millimole. I mean, that's a lot of glutathione, a tremendous amount of glutathione. It is one of the major detoxifying agents in the body, all right?

Does it detoxify other agents? Absolutely. Not only metals, but many other agents. Glutathione is one of the major endogenous detoxifying agents that we have. Ten millimole is no small amount.

Q It's a huge amount. Is that correct?

A It's huge.

Q So if the levels of glutathione are so low as to cause --

A So low?

Q So low hypothetically. If your levels of glutathione are so low that you cannot detoxify the amount of ethyl mercury in a mercury-containing vaccine, how could you detoxify any other substance in your body?

A Who says the glutathione level is so low that it cannot detoxify things? I don't know.

What you must say is the glutathione level in the plasma is very low. You're quoting Jill James or you're referring to Jill James' work. She did not do liver glutathiones. She did not do brain glutathiones. She did red cell. No, she didn't even do red cell glutathione.

She studied plasmic glutathione, and, as I and everyone else have told her, plasma does not have a high level of glutathione. Most glutathione is an intracellular compound. Very little glutathione is found extracellularly. I don't know whether that helps you or not.

Q No. It helps me. Thank you.

A Thank you.

MS. RENZI: I think that I'll break here for today.

SPECIAL MASTER HASTINGS: All right. Thank

you.

MS. RENZI: Thank you, Special Master.

SPECIAL MASTER HASTINGS: Thank you very much.

MS. RENZI: Thank you, Dr. Aposhian.

SPECIAL MASTER HASTINGS: Dr. Aposhian, thank you. You're done for the day, but we'll start with you again at 9 a.m. tomorrow morning.

THE WITNESS: Okay. Thank you.

SPECIAL MASTER HASTINGS: Counsel, before we go off the record is there anything we should talk about before we break for the day?

MR. MATANOSKI: Not on the record, sir.

MR. POWERS: Nothing for Petitioners.

SPECIAL MASTER HASTINGS: Okay. We are done for the record for today for those listening at home. We will start again at 9 a.m. Eastern time tomorrow morning. Thank you all.

(Whereupon, at 5:40 p.m., the hearing in the above-entitled matter was adjourned, to reconvene at 9:00 a.m. on Tuesday, May 13, 2008.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 03-584-V, 03-215V

CASE TITLE: In Re: Claims for Autism

HEARING DATE: May 12, 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 12, 2008

Christina Chesley
Official Reporter
Heritage Reporting Corporation
Suite 600
1220 L Street, N.W.
Washington, D.C. 20005-4018