UNITED STATES
COURT OF FEDERAL CLAIMS

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

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Courtroom 402
National Courts Building
717 Madison Place NW
Washington, D.C.

Thursday,
May 29, 2008

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

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

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C O N T E N T S

E X H I B I T S

PETITIONERS' EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
11	3949	--	2007 Laurente et al. Paper

P R O C E E D I N G S

(9:00 a.m.)

SPECIAL MASTER HASTINGS: We're ready to go back on the record on this autism proceeding in the King and Mead cases. Counsel, is there anything we need to take care of before we get started?

MR. MATANOSKI: No, Your Honor.

MR. POWERS: Nothing for Petitioners.

SPECIAL MASTER HASTINGS: All right, I see Dr. Deth is back in the witness chair. Welcome back, sir.

THE WITNESS: Thank you.

SPECIAL MASTER HASTINGS: You're still under oath from your previous time.

THE WITNESS: I am.

SPECIAL MASTER HASTINGS: So Mr. Williams, please go ahead.

MR. WILLIAMS: Thank you.

Whereupon,

RICHARD DETH

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

DIRECT EXAMINATION

BY MR. POWERS:

Q Good Morning, Dr. Deth.

A Good morning, Michael.

Q I'm going to try and run through several very specific criticisms that were made of your testimony and your work by the four different experts that the defense called to critique your work.

First, Dr. Dean James talked about how much glutathione there is in the human body, and how the amount of glutathione is so overwhelming compared to the amount of mercury that the thimerosal-containing vaccines would deliver; that it would simply be able to take care of it. What is your response to that critique?

A Yes, I had a chance to review Dr. Jones' testimony and comments, and I certainly indicated my respect for the body of work that he's done and the facts that he's assembled here.

Q The issue about how much glutathione there is in our bodies versus the amount of mercury that's delivered in thimerosal injections, for example, is an issue of stoichiometry. That is, the thimerosal mercury is not interacting stoichiometrically or one to one with the glutathione. This was never a premise, for example, of the theory or the mechanisms that we've put forth or that I've put forth in my testimony.

Moreover, the ability of mercury to remain in the body and to enter the brain, as has been verified in many

studies shows that the vast amount -- and there is a vast amount of glutathione available -- is not able to overwhelm this mercury and make sure that it doesn't enter the body or enter the brain. It's there; and because it's there, it causes effects.

Now Dr. Jones seemed to, in developing an argument or thought -- that because there's just so much more thimerosal quantitative, that it would swamp out the mercury, even though that's a simplistic thought.

Q I think you meant glutathione. You said thimerosal.

A Excuse me, the glutathione would swamp out the mercury or the thimerosal. The target of the thimerosal, or the inorganic mercury it releases is not glutathione itself. There's a lot of that. But the targets, the proteins, that it eventually binds to in the brain, inside of astrocytes and neurons and microglia, those targets and the amount of them, the proteins that are regulatory, those are in the small quantities.

So the really more valid question that Dr. Jones didn't exactly raise himself was, what's the proportion of targets for mercury in the body that have the highest affinity for mercury; and what's the relative amount of them versus the amount of mercury? Is there enough mercury to saturate those targets and to bind to them? These are

protein targets. They're not glutathione.

Q Now the adult monkeys that we know were covered in the Charleston Burbacher studies back in the mid-1990s, did those adult monkey brains have glutathione in them?

A Surely they did; all cells of the body have one to ten millimolar glutathione in them.

Q Yet, we know the mercury from those studies was able to provoke neuroinflammation in those monkey brains.

A That's right. So the point I just made, that the provocation of the inflammatory response is not because there's so much mercury that it depletes the glutathione one for one, that's not it. It's because those critical regulatory mechanisms are built upon sulphur and thiols binding the mercury, and it's their interaction that's causing the inflammation.

Q Now he also said that because of the dietary intake of glutathione -- and he gave an example of drinking apple juice would deplete glutathione and knock it down. What do you have to say in response to the apple juice example?

A This would be a blow to the apple industry, of course, if we decided to equate drinking of apple juice with the ingestion of mercury. It's just obviously nonsensical in space. But the transiency of the apple juice response, quite frankly, I'm not a nutritionist and I'm really not

that familiar with what it does.

But the idea is that there are fluctuations in glutathione levels as a result of diet, what we take in, as certain oxidative demands that it increases. So undoubtedly, there will be shifts in the amount of glutathione measured in the blood in particular. Because after injection, there is where the impact of what we just ate is felt, in the blood steam.

Inside of cells, it's going to be less so. In other words, if you biopsied a liver after drinking apple juice, you probably wouldn't find the same fluctuations you find in the blood stream, for example.

I'll offer further that because the brain is behind the blood brain barrier, protected as it is, it would be even less likely than peripheral tissues like liver to show fluctuations in response to diet.

So those things can occur. They're an important part of nutritional status. But they're certainly a whole difference realm than the effects of a prolonged agent like mercury. I just had apple juice, at breakfast this morning; by now it would have disappeared. It would be metabolized.

If I ingested, I'll be buried with the mercury, because it just doesn't change. It's always mercury. It's always there.

Q Now either Dr. Jones or one of the other of the

four experts also said that depressing glutathione actually provokes a protective response by the body. What's your response to that?

A We're well aware of the adaptive responses that are inherent in the so-called redox system of the body. It's really very interesting. It's critical for life, that you have the ability to adapt to stressors.

The adaptation could be very short term. It could be moderate. It can be long-term. There's a whole series of adaptive responses; and they're all designed to bring the system back to homeostasis. This is a classical word for like normal metabolism, normal function.

In fact, the redox system, in my opinion, is primary. I think it's the most important evolutionary factor that maintains homeostasis. So no doubt, when you shift it one way, you bounce back; and the reason you bounce back is because adaptive responses have been generated to help bounce back.

But some people don't bounce back. When you have a limitation in the system, perhaps in this case introduced by a burden of mercury, a persistent burden, your adaptive responses are trying to bring you back to normal. But you remain in a stressed state, where the sulphur resources are, in some cases, desperately trying to bring back the glutathione levels to normal. But you're not able to do

that.

It's really an inability of the individual with the autism and other related oxidated stress disorders, of them for their own reasons, partly genetic, that they're unable to bounce back and otherwise return to homeostatically normal conditions, that leaves them in a persistently abnormal state; a state of oxidative stress that unfortunately has with it a loss of function on a tissue by tissue basis.

So sure, there's adaptive responses. But usually they're short term; usually they're sufficient to bring you back to normal. So when you're not brought back to normal, you have persistent inflammation, persistent oxidated stress.

Q Now I want to turn to some specific scientific criticisms of some of the slides you showed and the data you produced. First, your slide 28 was about some kind of radioactive labeling of the methyl group. I think that's the right slide.

A I have 28 in front of me. I believe 28, maybe this is different numbering -- but my recollection of this criticism had to do with -- let's see, I think 28 is numbered on mine. Can we go to the next slide, if I can suggest, maybe a slide further? That's the one. That's correct.

I believe this result, which I have labeled 28 on my set of slides here -- I'm sure that this is what the comment was directed toward. So the comment that I'm going to try to illuminate or respond to was, why would the blue lines in this graph -- and what we're looking at here are graphs of the enzyme activity of the enzyme methionine synthase, the B12 and folate dependent enzyme. We're measuring its activity.

The blue lines in each case represent the activity when we're giving methyl B12, or methyl cobalamin. Noticeably, the blue line is higher than the red line. The red line is with hydroxy non-methylated B12. So I think the criticism or the question -- it was really a question of understanding, why would the blue line be higher if radioactivity incorporation into the methionine was the assay? Because the radioactivity is not present in the methyl group of the B12 here.

So the blue line, if you will, has got the non-radioactive carbon or methyl group in it, why is that activity is higher, it's not radioactivity. The radioactivity comes from the radioactive carbon group that's in the folate molecule that's a co-factor for this reaction.

Now the reason that the blue line is higher is because the oxidative conditions in the assay or in cells by analogy turns off the methionine synthase by oxidizing the

cobalt. I explained this and reviewed this in my presentation.

When the cobalt is oxidized or turned off, the enzyme stops. It has to be restarted, jump-started, like you're jump starting your car or something like that. It has to be re-started with methyl cobalamin, and the methyl cobalamin in this case can come from the methyl B12 that we add.

Once you restart the enzyme, it will turn around and turn over maybe 100 or 1,000 times, using radioactive methyl folate to carry out the reaction. However, if you don't have enough methyl B12 to jump start it, in effect, the radioactivity enzyme stays off, and the radioactivity does not get transferred.

So the reason that the methyl B12 blue curves are higher is because it's got the jump start material, if you will, available. As I pointed out, in the cells and in the brain, the availability of that jump starting methyl B12 depends on glutathione levels. If you don't have enough glutathione, you can't jump start the enzyme as quickly or efficiently.

So in these cells, as with the red lines here or in the brain, where glutathione levels are lower than normal, the enzyme will stay off more than normal. You'll have a methylation defect as a result of that. So oxidated

stress translated into impaired methylation.

It's a long winded answer to the question. But it's because the radioactivity reaction was jump started or re-ignited, if you will, by the methyl B12; whereas, the hydroxy B12, especially when metals are present, is not able to do that.

Q I think specifically Dr. Johnson said that he couldn't understand how you could measure one of these, because you were donating the radioactive labeled methyl group to another protein; and therefore, once it had been transferred, you couldn't measure the protein it came from. What the response to that?

A Well, I hope that he knows the reaction well enough to know that the source of the radioactivity is not a protein. It's the co-factor folate or methyl folate. So the transfer of the radioactivity ends up being too homocysteine, which is converted to methionine by the enzyme. Methionine is not a protein either. It's an amino acid.

So basically, we're looking at this reaction. The radioactivity starts with the co-factor, methyl folate, and this is the standard way of measuring this enzyme. Most people measure it the same way. It's written up that way in the literature. So the radioactivity is going from folate to methionine, and it's only intermediately attached to the

B12, which carries out the transfer in an intermediate way.

So there's no protein to protein transfer at all here; and I have to say bluntly, I'm not sure that Dr. Johnson in this case had a clear view of the assay, and also a clear view of how the occasional need for methyl B12 would actually make the enzyme work better; which is really why the blue lines are higher than the red lines on a regular basis.

Q Okay, now another specific criticism was, if I have the right slide number, of your quality control concerning your PCR technique on, I think, slide 34. Let's see if that's the right slide.

A This says what I believe is, we had several slides in which we used PCR to measure the messenger RNA levels of, in our case, methionine synthase, in the brains of autistic subjects' post-mortem samples.

We obtained the cDNA already available to us. That is, the way the PCR works is, the messenger RNA in the sample is converted in the laboratory to cDNA by a reaction, and that reaction yielded the cDNA, complimentary DNA as it's known. That is really what you then had to amplify in the PCR reaction.

In fact, for the autism studies described here, we received the samples from Dr. Persico in Rome, who made the cDNA from the messenger RNA. So that part was already

done. We received the cDNA, and carried out the PCR reaction for methionine synthase.

As a quality control measure, as we did and everybody does, and it wasn't evident in the slide because it's routine, one also amplifies at the same time another messenger RNA that's been converted to cDNA.

In this case, we used a so-called GAPDH that is a glycerol high phosphate dehydrogenate. It's called a house keeping gene. It's always on. So its levels can be considered a standard or a control. Then you always express, as we did here, the amount of the methionine synthase. There's a ratio to this always-present GAPDH. So that normalizes to any variations that might occur and that extract messenger RNA. This is a standard way of expressing this data.

So this data has indeed been normalized to a standard, as I just mentioned, even though it's not expressed explicitly here. It was meant to present the comparisons between autistic a non-autistic individuals. Of course, the difference is significant as indicated here, and indicated in the other slides.

Q Now this is still work you have not yet published?

A That's right. This is work done relatively recently, and we really anticipate submitting this for

publication in the next, I would say, two months to be practical about it.

Q In fact, I think you told me, you've got two papers that are about to be submitted on your recent work, that you described when you were here last week.

A Part of the reason that we have not yet submitted it, as we went along, was because the information fit together. We found ourselves wanting to sort of be more complete in our understanding of these changes in the sulphur metabolism that occur; not only with thimerosal exposure.

But it really is a much more global question of showing what the enzyme in methionine synthase and methylation is in general; in the brain, in particular, and neuronal cells, in particular. It is very much tied to redox the status and to glutathrone levels.

So as we went along and did that work, we needed to have that rather important -- I consider it important -- story complete. There's no sense in going in and getting piecemeal part of the data. So we needed to have, I guess in our opinion, a more satisfying story, which only gradually accrued.

For example, we take measuring the process of cysteine uptake, in showing that that was sensitive to redox and heavy metals. That was a recent work.

Then the autism brain studies that I reflected on here just a second ago describe that. Those are quite recent, also. They certainly reinforce the idea that this work, most of which was done in vitro in cultured cells, does have relevance to the intact brain; and even the intact human brain, and even the intact human brain in autism.

Because of that work being somewhat distinct from the in vitro work, we are now going to divide that into two sections; one dealing more explicitly with the human brain results that we got, and the other focusing more on the in vitro studies and the requirement for methyl B12 in neuronal cells.

Q Now while we're talking about brains, Dr. Johnson was also very critical of you for having used a graph that was built on data from a paper, and you did not give a citation for that.

A Yes.

Q We'll call that slide up. This is the one that had duck brain along with other brains.

A Yes, I think he referred to it as duck data or something like that. It was playful. But what it is, of course, this data was from the literature. This is not my data.

Now we can see that the citation, having been returned to the slide, because in fact I provided it. This

is the citation, and I never meant otherwise to indicate that this was data provided as shown here.

In 1958, a comparative study, which was actually a table in that paper, when one goes back to that original paper, you'll find this data in the form of a table. I converted the numbers simply into a visual image of a bar graph here; and I did, in my original slide, have the citation very clearly as it's shown here, indicated. Because I think it's a very critical finding.

What it illustrates again, and that's not to be totally sort of confused or otherwise not recognize the importance of this -- the importance of this, again aside from where it came from, is the fact that the human brain status is very noticeably different from not only the other species, but noticeably from all the other tissues in the humans that were looked at.

So we can say to this, gee, there's something very unique about human brain with regard to its sulphur metabolism. So that was the point that I tried to make here, using this data, again from the literature.

Q In your lectures that you've given prior to your testimony here, was this the version of a slide that you always used?

A That is the case; when I first created it and every time, including last week at Autism I, when I

presented this slide again. That citation was very clear.

Q The citation disappeared after you gave us your slides.

A Somehow it did, yes.

SPECIAL MASTER HASTINGS: This was slide 17, for the record.

MR. WILLIAMS: That's right. All right, now you can take that down, Scott.

BY MR. WILLIAMS:

Q Dr. Roberts had a criticism of you. He said that you cannot reliably assess oxidative stress by measuring MDA; and he said that the TBARS test was unreliable. Do you recall that?

A Having read his testimony, as well as his expert opinion, I understand what he said. It doesn't have much or actually any relevance to my own work and my presentation. He is, I guess, raising issues about the definition of the state of oxidative stress, for reliability of one versus another marker or bio-marker.

Because a lot of oxidized products can be measured and will be higher in their amounts during oxidative stress. One is not perfect; one different than another. I'm sure in the field of people studying bio-markers that there's controversy about who's is best, which assay is the best.

We didn't do any of those. Our focus instead is on measuring the levels of the thiol compounds themselves; not to the products that might eventually be oxidized if the thiols are abnormal or if there's too little glutathione. We didn't do that, and so that criticism or that controversy has really no relevance to our work.

Q Now I think Dr. Roberts was the one who also said that you can't detect oxidative stress in the brain by looking at peripheral biomarkers in the blood. What's your response to that?

A I wouldn't disagree with that statement. If you want to verify oxidative stress in the brain, you have to look at the brain. There's different implications of that, and one implication I think he was getting at was if Dr. James in her work showed evidence of oxidative stress as a lowered ratio of the reduced oxidative glutathione in the periphery in plasma, does that necessarily mean that it would exist in the brain, as well?

It doesn't necessarily mean that. You have to separately measure that. But the fact that the plasma is indicating very significant signs of oxidative stress at the level of the thiols is creating a very likely hope that the brain will also show that.

Because the plasma reflects the metabolic state of the liver. When it comes to thiols or sulphur compounds,

the liver, that is the main metabolism organ that we have and is almost in control of plasma levels; and the liver is also the source of the sulphur resources for the brain.

It's the liver that releases cysteine, oxidized cysteine. It's the cysteine that crosses the blood brain barrier. It's taken up by glial cells and astrocytes that ultimately provides the cysteines to neurons and to the brain in general.

So when the plasma levels are showing lower levels of, for example, cysteine with the liver not providing enough to keep the plasma level up, you can imagine that the brain is seeing that reduction as well, and that the levels available for the brain are less. So even though you can't confirm that the brain is showing oxidated stress, you can certainly expect that from a lower plasma level.

Now separately in studies of the brain, and I'm thinking here mainly about Dr. Pardo's studies, that looked at the brains of autistic individuals, post-mortem samples certainly show the signs of oxidative stress and neuroinflammation in that organ in the affected individuals who are the subject of this proceeding here.

So there is no doubt there is oxidative stress and inflammation in the brain; and this would be true also of the mercury-fed monkeys, where the sign of activation of

microglia and other signs in the brains of those monkeys showed inflammation in there.

So it's a bit of a straw man to say, oh, there's no oxidated stress. How do you know there's no oxidated stress in the brain? It's been measured. It is there. So these are just sort of the background issues. They're all in place to confirm that there is inflammation and oxidation in the brain.

Q Have you actually published your opinions about the relevance of Dr. Pardo's neuroinflammation autopsy studies to your oxidative stress model?

A Being aware of all these issues for the last several years, as our work moved in this direction, I published a peer-reviewed article that was in the Journal of Neurotoxicology this past early, I think it was, January, that was actually released.

So this review article shown here entitled, "how environmental and genetic factors combine to cause autism a redox and methylation hypothesis." I attempted in that article to include the work of Pardo, but others as well, that document is in the literature the presence of neuroinflammation and oxidative stress in autism and in the brain in autism.

Q Let me get to this. This is Petitioner's master reference number 563.

A 563.

Q This journal, by the way, what is this journal, the Journal of Neurotoxicology?

A Well, in the field of toxicology, there's a subdivision, neurotoxicology; and there's a society of neurotoxicology, and this is the journal that sort applies the journal for that subdivision of toxicology and that society.

Q Then if we turn to page six of this paper, if you highlight the lower right hand column from the bold on down, is this the section of your paper where you discuss oxidative stress in autism?

A That's correct.

Q At the very bottom, do you see where it says, elevated levels of inflammatory cytokines and evidence of microglial. Then we have to turn the page to page seven, and if you'll blow up the rest of that paragraph please, Scott, microglia activation -- I guess there's a typo there. The two words "microglia activation" are repeated -- was observed in post-mortem brain section, indicating the presence of neural inflammation.

Then you cite the Vargas paper which, of course, Dr. Pardo was the senior author of, correct?

A Correct.

Q Then you cite the adult monkey studies done by

Burbacher and others back in the 1990s, correct?

A Correct, as well as preceded by the other references having to do with the biomarkers of inflammation and oxidated stress.

Q Now Dr. Roberts also said that oxidated stress is the body's normal healthy protective system; that we need to have oxidated stress in order to react to insults. What's your answer to that criticism?

A Well, it's not a criticism. I think it's a fair and a correct scientific statement. I've come to appreciate that as a question of the details of how does that play out; who are the players in these adaptive responses to oxidated stress? We certainly do that, and it is important.

Nature has availed herself, if I can use that, out of the importance of this in terms of a great deal of complexity in the many different ways that we do respond to stressors; not just of an oxidated nature, but things that impact on us that ultimately can use that same system as an adaptive system. So yes, it's very important and it's very complex.

Q How can oxidative stress then become a hazard to us?

A Again, I alluded to this a little earlier. My view of that is that cells, and I don't think I included a side view, but in fact I have one that I'm mentally thinking

of here, that cells normally operate at a normal redox set point. It's appropriate for that cell, that function.

But oxidative conditions shift the redox set point to a different value that's a more oxidized value. This is what stress does. It could be a foreign intruder like a bacteria or a splinter or something like that; some event that's a stressor.

So the cells, they adapt to that and they mobilize their metabolism to offset that distressor and hopefully resolve it. They do that by shifting gene expression, and methylation is how they do that. They do that by cytokines release that attracts white blood cells. So it's a lot of adaptive responses. Usually, those situations resolve, because the adaptive responses have been successful in dealing with the stressor source.

Then the mechanism is reversed. Methylation returns to normal. The cytokine production goes back down again, and we're back to business as usual in a certain way. That kind of adaptive mechanism is really very critical.

However, the ability to move back again depends on having adequately resolved the oxidative stress that's the trigger for these adaptive responses. If for whatever reason, and xenotoxins or toxic substances that interfere with sulphur metabolism problem here -- if you're not able to move back again to restored normal function, you remain

in this adaptive state, and it becomes a maladaptive state. It gives rise to chronic diseases, chronic conditions, and then there are many of them.

Almost any inflammatory condition and this type of a disorder would be an example of a chronic inflammation state; and the failure to resolve that and come back to normal gives chronic diseases. In the case of neurological problems like autism, that's reflected likewise as a loss of function associated with a chronic oxidatively stressed state, which reflects an inability to return to normal.

Q Can inorganic mercury in the brain create such a permanent oxidative stress state?

A That's right. The key thing is that it represents a potential stressor, sure. But even more important, in my opinion, is the fact that it defeats or interferes with the system that brings us back again to normal.

Indeed, for the case of, let's say, vaccine associated thimerosal and mercury exposure, let's say that all individuals experience some response to mercury in the presence of that; but that some of able to deal with it and they resolve it. Maybe they excrete the mercury, or maybe even if the mercury is still present, they have enough reserve to bring the system back to normal.

That is to say, their genes allow them a more

effective adaptive response, so they can handle higher levels of mercury. They may have some consequences, but not long term and not as severe. So in those cases, the neurological consequences wouldn't be as great. So the differences can be individual, and the duration of this and the role of mercury in particular, because it defeats the response system that's not only a stressor, but it defeats the ability to recover.

I think it is a little bit like the AIDS virus; that the AIDS virus interferes with our immune system, the very system that we rely on to deal with foreign invaders. So by inactivating that system, the AIDS virus is going to be persistent, because we can say, in a clever manner, it has interfered with our ability with our ability to deal with its very presence.

Q Now another specific criticism, and I think this was from Dr. Mailman, was that in your cellular model, you didn't have copper involved. In the body, copper is present and provides some protective mechanism from oxidative stress. What's your response to that?

A Again, I respect the perceptiveness of that comment, because copper is a player in sulphur metabolism and in redox regulation. In our own studies, Waly et al. that we published, we had a series of studies with copper and its oxidized 2-plus or reduced 1-plus states. We showed

opposite effects of those two states of copper here.

As it turns out, copper is a counter-balance to the cysteine, and in its oxidized and reduced forms the two are exchangeable. So you can shift the copper to its reduced form, at the same time you're shifting the cysteine to its oxidized form. The two of them can reciprocally interact.

So in a case, copper is an important factor, and I acknowledge that. Now in our studies it was not, with the exception of those experiments, a variable. Certainly, we didn't, as I said, include it; nor did we include zinc or any other important additional factors as a supplement.

But the way our experiments and everybody else's are done in cultured cells is, you have them in a media; and the media contains the basic cells and nutrient materials that are shown from a chemical origin.

Then you add in, let's say, 10 percent fetal bovine serum or fetal calf serum. This is the key ingredient to allow the cells to divide. That really represents blood and serum, and contains all the things that are in blood and serum, as it comes along, which includes some sort of copper, as well as everything else that's in there. So our cells see copper routinely as a matter of their exposure to the 10 percent fetal calf serum.

We don't go out of our way to change that. It

wasn't the variable that we were looking at. But we do acknowledge that copper does have effects on non-sulphur metabolism.

Q Now there were a couple criticisms of one of your slides where you were measuring the change in glutathione in relation to thimerosal exposure.

A Yes.

Q Let me pull this. I think it's slide 24, if I have that number right. Yes, I believe it was this slide. The first criticism from Dr. Jones was, he said that he had devised at least one test to measure glutathione; and that he couldn't understand how you could measure glutathione at .1 nanomolar level. I think you said this several times. What's your response to that criticism?

A This was confusing to me. I don't know if Dr. Jones again was setting up an experimental situation which did not apply to us. He seemed to be saying, well, if you're seeing effects of thimerosal at 10 to the minus 9th, or nanomolar level, that must mean that your measuring somehow changes of glutathione in that same concentration range.

Again, it's as if one molecule of thimerosal was interacting with one molecule of glutathione, and that's not what we were measuring. That's not what happens.

As a matter of fact, if we look at the "y" axis

here, the vertical access, you can see that the molecule 750 is the intercept there per milligram protein, and just goes down from 750, I suppose, to 350 a 300 nanomolar, change associated with that 10 to the minus 9th or one nanomolar concentration of thimerosal.

So even on the face of this graph, a 300 moles per milligram change of the glutathione for one nanomole change of presence of the thimerosal; so right away, as we have recognized, it tells you that it's not a one for one change in the glutathione. So we're not measuring minute changes in glutathione. They're major changes, you're looking at 40 percent decrease or 50 percent decreases in the amount of glutathione; way beyond what that molecule of thimerosal could ever do itself.

That's why it points, as I have said several times, to the fact that it has a big multiplier effect, because it's actually affecting regulatory proteins like thyrotoxin reductase, which are many times over-affecting the glutathione states.

Q I think Dr. Johnson also had a criticism of this particular experiment. If I understood him correctly, what he was saying is that in this particular line of cells, glutathione is not present at the levels that you claim to be detected, that it's lower.

A I heard that comment off of his testimony and I

take it to heart, and I actually only heard it, quite frankly, last night. And I checked myself, also looking in the literature, and I found papers that had actually higher levels, and I found a number of papers that had lower levels than this. I feel incumbent on me to go back to the lab and to respond to his comments by checking on the calculation that goes into this left hand axis number.

But no matter what that is that might allow that possibility, there might be something to look for there. But the effects of thimerosal, no matter what the absolute number is, are obvious.

They're not only obvious here. There's a 40 percent decrease from whatever the absolute number was on the left hand axis, which is important and I do need to address that. But the cause is obvious.

Moreover, this measurement of glutathione, as I presented, is only like a middle step, or one of the three or four or five different steps in the process that are all showing the same dose response relationship to thimerosal. So the glutathione levels, per se, are only one of a pattern of activities that reflect the interference of the sulphur metabolism of the thimerosal.

I might also add that glutathione is very easily converted to other things, when you stop a reaction. You'll have the highest levels of glutathione at the time the cells

are healthy and normal.

Then when, in the way experiments are done, you then stop whatever treatments are taking place; and then you go ahead measure the glutathione, which takes a certain internal of time, that interval of time no doubt is associated with some loss of the glutathione, and because of its nature it's unstable.

So although I take to heart those comments, the higher levels are associated with the most efficient measurement of the true values. They're not going to go up, experimentally speaking. They can only go down. So in effect, we have higher level, which at least puts us on the better side of that relationship.

Q So even if you have the wrong absolute numbers here for glutathione here, because of a miscalculation of some kind, the relative change is what's important. Is that what you're saying?

A Well, the relative change is important. I'm not acknowledging, because I don't know this to be the case, that this is somehow erroneous. Although because of this collegial criticism, I understand that I need to go back and check and double check to make sure that that's the case; and we have checked. It's not like I don't check these things.

But nonetheless, whatever that outcome may be,

the experiment the way it was done, still leads to the fact that there's a 40 percent change or a 50 percent reduction caused by thimerosal, no matter what the absolute value is ultimately determined to be.

Q Now related to that, at least I think it was Dr. Jones said that you could -- manipulate may not be his term. But in your cell culture, you've got the fluid above the cells, and you have a certain number of cells in the dish. He suggested that by changing the volume of the fluid above the cells or by changing the number of cells, you would affect the concentrations within the cells in sort of an artificial way. What is your response to that criticism?

A Well, with these experiments, just like everybody else does experiments with the culture cell system, typically, the cells are grown until they are so-called confluent. That is, there's like a carpet or a single layer of cells at the bottom of the well in a petri dish or something like that.

Then you add a solution to it to measure the biochemical things that your experiments are designed to look into. So we didn't do anything unusual here.

The volume that you add can be, I guess, varied. There has to be enough to cover the cells. Just to be specific in our case, in the wells that we do these experiments, typically you need 600 microliters as minimum.

That's two thirds of a net ML at a minimum, just to keep the cells wet above them. We use two MLs. That's about three times that, as a standard volume.

So in any case it's not extraordinary, we didn't like rig the system or something like that. That is large volume. It's typical that there's a volume above the cells.

He made the point that mercury has made some special properties. That is to say it has a high affinity for thiols. This is where this whole thing starts from. So cells that contain thiols will bind the mercury.

Once the mercury is bound, it's no longer free. So we have two different states or forms. The driving force for the movement of anything, mercury included, as an ion across a barrier from one side to another or from the fluid into the cells, is driven by the concentration difference. And as the concentration outside is high, there's a natural tendency to go into the cells because it's zero inside the cells to start with. Now when some gets bound, some more will replace it. So over time an equilibrium will be established with bound mercury inside of the cell, free mercury inside the cell, free mercury outside the cell.

Now our experiments are done with relatively short time intervals. That is one hour. We're looking at the earliest things that mercury does. We could look at longer times, but what are reported here are the first

things that mercury does. So we typically have one hour of incubation, and then we test what the cells are like after that hour.

I'm sure, if we waited longer, we would get to that equilibrium in the end. But at the time we're doing these studies, we're probably still looking at the initial stages of mercury moving from outside to inside; and there's still plenty of mercury outside. He made it sound like there's a vacuum cleaner effect where the cells are sucking up all of the mercury from the fluid around there; although I don't believe that's true. I think it's a concept that somehow it be a criticism.

But the amount outside is still going to be outside the high concentration. But the cells have taken up some, and some has been bound. Let me explain just a little further to say, the bound is going to be found at the highest affinity sites with the greatest probability. You have binding sites for mercury; some of which are extremely high affinity, and they'll have the first priority. Then you have weaker binding sites that have less priority.

If you're wondering where the mercury ultimately will be, it will be at equilibrium in long term in our bodies at those high affinity sites, and those are the targets that I'm referring to when I talk about targets of mercury and regulatory proteins. Those will be where the

mercury ends up.

Q Now there were a couple criticisms of tables or figures you've used from Jill James' papers. In particular, Dr. Jones said, he pointed to a set of genetic variations. Exhibit 49 is the paper, and it was one of your slides, also.

A Perhaps slide 39 or something?

Q Yes, I think that was the right table, wasn't?

A No, he was talking about genetics. It would be a much larger slide.

Q Yes, this is another one we have to deal with. But let's stay with the genetic one.

A I believe it was the second to last slide that I had, if I'm not mistaken. Yes, it's that one.

Q Okay, this is the right one now. What he was pointing to, he said that some of the changes here showed a protective effect of these genetic markers, as opposed to a risk effect. What's your response to that?

A Well, what we're looking at here are six different genes that have six different polymorphic states.

SPECIAL MASTER HASTINGS: This is slide 39, correct?

THE WITNESS: Slide 39 for the record here.

So the six genes that are displayed here, and their differential occurrence in autistic versus non-

autistic subjects, that's what this is about.

BY MR. WILLIAMS:

Q Okay, now the six genes are in the left hand column?

A That's correct, and their abbreviation is in the white box, which is from the paper, abbreviated with these short letter abbreviations.

Q And then each of those genetic genes have different variations themselves?

A Right. For each of these, there's more or less two possible states. For example, in the top one, the location of interest could have an "A" as a nucleotide adenosine or a "G", a guanosine. So it's either A or G and so forth for the others as well. So the alternative gene states are single nucleotide polymorphisms. That is a variance of a single nucleotide, A or G in this case.

Q Then you have AAGAGG. What do those signify?

A Because we have two copies of each of the genes on two different chromosomes, then you could have your same A on both of them. You could have an A on one, a G on the other, or you could have two Gs. So this would be the possibilities that are displayed here.

Q Then what do you have as bolded, or what does she have?

A Well, what does she have, yes, right.

Q This is Jill James' table.

A As it indicates in the small print at the bottom, its significant and border line significant differences are in bold type. So this is meant to highlight those that either were or met the statistical criteria of a P value less than .05; or in particular, that the odds ratio, the right hand column here did not, in some cases, almost did or did not intersect with one, which would indicate one would be just sort of the normal equal occurrence in autism and controls.

If there was a significant difference than one odd ratio, that would mean a difference, and they're favoring the autistic population rather than non-autistic population.

Q And if the confidence internals there in parenthesis in the right hand column include the number one, what does that mean?

A Well, that means they don't meet the criteria of significance, with that criteria being an odds ratio of 95 percent; that is, the chances being less than one in twenty of a random occurrence here. So they don't meet the criteria for significant differences.

Q In some cases, because of the way she phrased that, significant and border line significant -- border line is a little wishy-washy. It's a little unclear. Almost

significant, I guess, is my take on that. It's allowed highlighting of things that approached, by some ambiguous definition significance, but not quite reaching that.

Q Are there any statistically significant values here in the relevant genes that are below one?

A I see several, actually. The ones that raised this particular issue or were raised have to deal mainly with the last one at the bottom, NTRR, or the methionine synthase reductase. So this gene, and its gene product protein, as the name implies, is involved in reducing the B12 in the methionine synthase, so the enzyme can be jump-started or reactivated again.

In non-neuronal cells, like the liver and so forth, this enzyme plays a major role. Our evidence indicates it doesn't play that same role in neuronal cells. But in any case, this one has the odds ratios, as we see .78, .69, .61, and .66.

From those, each of them is below one, and the confidence interval is right next to them. For example, for the .78, the confidence internal was .61, and it goes up to 1.02. So, it goes just above 1.0, and I think this is an example of a borderline significance that was alluded to in that descriptor there.

But taken together, these suggest but don't actually statistically reach that criteria. Because none of

them actually, in their confidence interval, exclude one. They all sort of wander slightly over one, and as a result, really, they aren't significant. These are all the lower line ones.

But nonetheless, because they're all borderline, they suggest that maybe having a particular form here of this enzyme or gene is protective; that the risk may actually be less if you have one of those. I would attribute that, if I had to speculate about the meaning of that, to the possibility that, for example, in non-neuronal cells like liver, kidney, or whatever, that if you have a certain form of this, then it has a contribution of a protective nature. If I were to take the border line and forget about that and call it significant, that's the interpretation I would give that.

Q Now another criticism, based on your use of Jill James' work, I think, was on slide l3, if I have the right slide number. Yes, and specifically, what I had written down is that Dr. Jones said that on this slide, the change in the cystathionine was protective.

A I'm going to let you restate that.

Q Well, you probably understand the criticism better than I do.

A I know, because I reviewed his testimony, and I know this issue was on the agenda here. I think he was

referring to the cysteinylglycine, which is roughly in the middle here, which shows a value here of 39.4 in controls and 38.9 in autistic population; clearly, no difference. Sure, on the right hand column where the significant differences are portrayed, it stands out, .78, as something that's not significant.

All the others are significant. That is, all the others are below .05, indicating they meet the criteria as statistical significant. So who was it, Dr. Jones that brought this out?

Q That's what my notes say.

A In any case, clearly, it's trying to call attention for some reason to the only one that wasn't different. So all the other ones are different and extremely different. So, I guess, we're going to end up sort of focusing on the one that wasn't different here, which is somewhat diverting, I suppose.

But the cysteinylglycine, if I reflect on why that might not be different, I think that's really what the question is; why does the fact that that didn't change, is that a dramatic finding, even though everything else is different? I don't think so. We're talking about the cysteinylglycine. The glutathione is missing the glutamate.

So typically, the glutathione is pushed out of certain cells. Let's say, in the blood, this might be blood

cells. Some of them released glutathione; or maybe the liver released glutathione.

Then outside of cells, there's certain peptidases that cut off the glutamate, leaving behind this molecule, which is cysteinylglycine in a dipeptide. Its levels don't change, despite the fact that everything else is changed.

I, quite frankly, don't know what to make of that. It's not a significant issue, in my opinion. But I guess it would indicate that this is not critical in autism. The amount of this is not critical in autism.

I'm certainly okay with that. But everything else is abnormal, and I have to say, that's really the message here. It doesn't make sense to focus on this one factor.

Q Now another specific criticism Dr. Jones made had to do with a receptor or transporter on the surface of the cell that you talked about, called EAAT3. I think we need to pull your diagram of the cell back up to discuss this. Which slide would best illustrate this?

A I'm looking at my cell slide 18, which I think is reasonable.

Q Now, if I understood him right, what Dr. Jones was saying is that you focused just on this receptor, but these neuronal cells or neuroblastoma cells have lots of other receptors that somehow make up for any problem with

this one.

A In the context of his remarks, yes, he was making like a general statement about cells. I don't know that he was specifically focused on neuromal cells; but, in fact, that's what this slide was meant to illustrate. We did work with neuronal cells. So my knowledge here is mostly about neuronal cells, and he is incorrect about that.

But even in studies in studies in mice brains, where the particular transporter here was knocked out, knock out mice that don't have that, there was a major decrease in the glutathione levels, and they suffered neurodegenerative consequences in their neurons.

Because in mature neurons, the literature indicates in that study and our own work supports the idea that the EAAT3 is the major, that is more than half, source of cysteine uptake or even cystine uptake, that is oxidized or reduced cysteine.

So it is both in the literature and explicit experiments, and when we studied this as I presented that data with thimerosal, we found that when we blocked with specific transport inhibitors of that transporter, and we blocked it, we blocked two-thirds or more, actually I'm being modest here -- at least two thirds of the uptake of cysteine was blocked when you blocked that transporter.

So clearly, it is the major source of thiols in

the form of cysteine to these neuronal cells, and the literature also indicates that in an intact brain, the same role is present.

Q So is it fair to say that his statement about other receptors or transport cites would be true of cells outside the brain; and it's not true of neurons?

A That is true. For example, astrocytes have a different transporter. The EAAT3 is not the most prominent in astrocytes. They have a form which takes the cystine and group and glutamate in opposite directions. So that's a different transporter than astrocytes, just by example.

So there is a whole family of transporters. He's certainly right about that. But let me get down to neurons specifically. The EAAT3 is the major transporter of interest.

Q Now I don't remember which of the experts on the other side said this, but you were criticized for even calling your cell model neuronal because it's some kind of specialized tumor cell from outside the brain. What's your response to that?

A Well, it's not a brain. We don't have a brain in a petri dish. We have a cell line. They arise from tumors. They are major, major tools in biology. Many people use these replicating cells as test systems, and they yield important information that can then be further considered or

followed up on it in other systems, such as primary neuronal cellcultures, for example.

But the cells that we work with, the so-called SH-SY5Y cells, are derived from a tumor, a neuronal tumor. They can be induced to give full fledged neurons with synapses, and like a neural network right in the petri dish. If we treat them correctly, they can do that; or they can be in a sort of proliferative phase, where they multiply more frequently. They are the most commonly used cell culture model for human neuronal cells.

We chose them partly for that reason. So they certainly meet the criteria of being in the field with a standard system to be used. They can be neuronal. They can be dividing. They meed to be both dividing and neuronal, in order to be useful in a cell culture.

Q Now one of the major criticisms that Dr. Jones had of your work -- in fact, I think he described it as unbelievable or incredible -- is the low dose of thimerosal at which you found effects. What's your response to that criticism?

A Well, I was impressed, from the very first time that we carried out these kinds of studies myself. If I looked back and said, when was that; that was back just in the year preceding the IOM considerations of the World of Mercury and Autism, the first paper, the Waly paper, where

we did those response curves that showed subnanomolar effects of thimerosal on phospholipid methylation, that peer reviewed paper. I was obviously impressed.

As a matter of fact, let me relate the reality of the situation. So as I recall, this was in the summertime, and these experiments were taking place. I said, my God, look at those potent effects of thimerosal, and this is the same thimerosal that people are worried about, or at least considering as possible risk factor for autism; and I know that there's a committee out there. The Institute of Medicine that's interested.

I had better contact them with this finding, because I was so struck by it. Being in Boston, actually the Chair of that committee was actually at Harvard public health schools. So I was on the phone, calling people to let them know about this.

I have to say I, too, was struck by the low concentration that was striking. Because they brought the potential for toxicity involving this system to a higher level of likelihood, than the other studies on other cell types and other end points that typically had micromolar inhibitory effects. We were, on the other hand, seeing nanomolar or even subnanomolar inhibitory effects.

So I can understand when somebody first sees this data, that they're saying, wow, what's this about? It seems

it is, number one, striking; and maybe it says to people, oh, I'm not sure whether that's true or not.

Likewise, replication; that's why we had to go back and look at all the things that led up to that observation and say, well, why does that happen? Why is it so sensitive? What is causing, in the case of the methionine synthase to be turned off?

Our first observation was that methylation activities are inhibited at these concentrations; all of them. Why is methylation inhibited? Oh, methionine synthase is inhibited. Oh, I see; that's why. Well, why isn't methionine synthase? Well, it must be because the B12 is affected. That's because the methyl B12 is not synthesized. Oh, let's measure that. That's down, too. Well, why is the B12? Oh, it's dependent on glutathione. Oh, the glutathione level is down. Why is the glutathione level down? It's because the cystine uptake that supports that is down, as well.

So as I indicated before, this is the sequence of events that we went through; and each one of those, as we worked backwards, showed the same nanomolar sensitivity in this systems. Of course, it lead to other studies, that we've done in animals; but now more importantly in human post-mortem studies in autistic subjects, to find that indeed this enzyme that shows nanomolar or subnanomolar

sensitivity is disturbed and subnormal in its levels in autistic brains.

So this again was a little bit of shock to me, and that's why we followed it. When you see something like that, you need to understand it.

Q Now after you testified here, and actually I think it was two weeks ago, did you find another paper that found effects of inorganic mercury at the levels that Dr. Jones was surprised at?

A That's right. Well, in reading Dr. Jones' testimony, actually it alerted me to Dr. Jones' work. Because actually, seeing first his expert opinion. I hadn't made the connection with his experimental work, which was mostly just sort of direct criticism of my own.

Now I realized that I, in fact, knew his work. In fact, his studies that showed the effects of mercury and a series of other heavy metals on thioredoxin, the regulatory protein that regulates cysteine oxidation was work that I had paid attention to. As a matter of fact, our lab at a lab meeting discussed his paper in some detail. Then when I appreciated that, in light of his comments, I recognized the thioredoxin was in fact a potential target of interest here.

I had proposed this here when I explained in my testimony about how mercury has two binding opportunities on

each side, especially inorganic mercury; whereas, the organic only has one. But once it becomes inorganic mercury, it can grab onto to two different cysteines, and the molecules that contain those two cysteines are just the right distance. That distance is about four ingstroms. I'll be quite explicit about that.

If you look at the structure of molecules, the distance is just enough so if a sulphur is here and a sulphur was there, a mercury could extend both of its binding arms to bind simultaneously to those two.

So I had proposed, as I thought about the ultimate targets, what they might be like for inorganic mercury. It would be a target that had two cysteines approximately that distance apart. When one looks at the X-ray crystal structure of thioredoxin, one finds cysteine number 32 and cysteine number 35 are exactly that distance apart. In fact, they can accommodate a zinc between them.

This is described. But instead, if a mercury is between them, the mercury more strongly bonds and stays there. So the one side breaks. Even on the rare occasion when one sides breaks and comes away from the non-cysteine, the other side is still anchoring it there. So it's just a matter of time until that other one reforms again. So this is a rather permanent, rather long-lasting, location for mercury of high affinity.

So with that kind of background, the thioredoxin and glutaredoxins, the two sister molecules, they both have a similar orientation, I suggested and I presented this in different symposia as targets.

Now a paper came out that I just actually found by PubMed searching; a paper in which indeed the effects or inorganic mercury applied to that particular thioredoxin, were in the same nanomolar range, the exact same nanomolar range; what we found inhibition of this human neuromal cell thiol metabolism.

Q Let me stop you. Let's pull the paper, so that we know what we're talking about here. I tried to discuss it with Dr. Jones. But he hadn't had a chance to read it or he hadn't seen it before, and he declined to answer questions about it. What exhibit number did you give this?

A Trial Exhibit 7.

Q Right, it's Trial Exhibit 7. So first, isn't it true that at least three of Dr. Jones' own papers are cited in the references of this paper?

A That's true, and it reflects a close working relationship, I suppose.

Q Where is this paper from? Is this from a reputable group?

A Of course it is. Both myself and Dr. Jones' know Dr. Holmgren's work is really exemplary.

Q How do the findings in this paper support your own work, your own conclusions?

A Well, the role of a thioredoxin is to regulate the oxidation state of thiols, cysteine in particular, in cells, which can be either oxidized, joined together, or separate. What the thioredoxin does, when it's thioredoxin in its reduced form, which is its active form, it's able to come into to oxidize cysteines and reduce than, so that they are no longer oxidized and they are reduced.

So the thioredoxin is oxidized. As a result, it has to go through a cycle and get ready to do the same job over again. So it takes oxidized cysteines, called cysteines, and reduces them.

Those cysteines can typically be in proteins, where they're holding proteins in a certain shape. Notice how my arms are sort of bent like this and are oxidized. But if they really weren't oxidized, my arms would be free to move, and the protein would have a different shape.

So really, what it's doing is affecting the shape of proteins by converting oxidized cysteines to reduced ones. This is how nature regulates many proteins, many proteins, thousands of proteins.

So when thioredoxin is not working, then in fact those same thousands of proteins would be more likely to be in their oxidized state, rather than their reduced state.

Accordingly, their activity will be different. There's a very powerful enzyme or small enzymes that does that job.

In addition, in diagrams that I have used, I have talked about how the oxidized cystine or cysteine that's taken up by astrocytes or glial cells; and in the case of astrocytes, they are able to reduce it and convert it to glutathione, which eventually the astrocytes give out to the neurons nearby.

If the astrocytes thioredoxin is not working, the cystine that they take up is not reduced. As a result, the astrocytes will suffer problems from not being able to make enough glutathione. Secondarily, the neurons that depend on the astrocytes will suffer from a lack of cysteine and a lack of glutathione.

So the thioredoxin is important in several ways. It's important in regulating proteins' shape and activity in many enzymatic ways. But it is particularly important in supplying the cysteine necessary for glutathione synthesis in astrocytes and in neurons, as well.

The particular features that render it highly sensitive, as this paper pointed out, it is quite remarkable to me to see this paper. By way of background, when I saw Dr. Jones' paper and we discussed that at our lab, I said, oh, thioredoxin looks very important. We should recognize thioredoxin. Let me look into the literature of that point,

which was about six months ago.

I contacted Dr. Holmgren by email, and I said to him, do you think there might be the possibility that mercury could interact with thioredoxin in a potent manner. I described our work to Dr. Holmgren. He said, oh, you'd be surprised. We've already studied that. We have a paper coming out, but he didn't share that with me.

So I knew that in the pipeline there was, at some point, going to be a paper about mercury and thioredoxin. But it wasn't until a week ago, after my testimony here, that I was able to see this paper and what he meant by it.

I further suggested to Dr. Holmgren, and I haven't heard back from him, that the human neuronal cells, as opposed to the other cells that he might have been working with, might have an even higher sensitivity because of, as I pointed out here, the properties of neuronal cells and of human neuronal cells, that put them in another echelon of oxidated stress or risk.

So I suppose, and I'm waiting for him, I understand that he is undertaking further studies with the same cells that we have worked with, to further test that. That is the last email that I had from him. The study was very important, and I just, however, became aware of that after our previous testimony. Otherwise, I would have included it.

Q If we could just quickly look at figure 1, Scott, which is on the fourth page of the exhibit. Does this show effects of inorganic mercury at the same nanomolar levels that you have been finding effects?

A Yes, particularly the inorganic mercury in the top part A here, is the line sloping downward on the left, which is more potent in this case than the methyl mercury. Again, I would say the inorganic mercury has two arms. The methyl mercury has one arm. They are both able to inhibit here. But the effectiveness of the inorganic mercury is higher, and the concentrations they inhibit, they describe as having an IC50 of the approximately 10 to the nanomolar level here; meaning that the inhibition is occurring at even subnanomoric concentrations. Ten is like the mid-point here.

Q Okay, now you can take that down Scott. Another critique of your work, this was from Dr. Johnson. It was not your work. It was a critique of Dr. Hornig's paper. Dr. Johnson showed some pathology slides from her paper on those SJL mice; and then compared it to the pathology slides from the U.C. Davis Group. First off, that paper, I think, is Berman.

He was very critical of the pathology work done by Mady Hornig's group. Do you have any response to that criticism of her work?

A The comment he made I think was about the histochemistry staining. I'm not really an expert about that. Quite frankly, I looked at the figures, in Mady Hornig's paper. I could see visually myself differences in the ones that I paid attention to most.

For example, in Mady Hornig's study, the one that I did pay attention to most, was the one where she had the EAAT3. That is she did an immunohistochemical staining for that very cysteine transporter that we just talked about, unbeknownst to her, it's a cysteine transporter. She considered its other role as a glutamine transporter.

What she found, and what I was convinced visually by the evidence that she presented, was that that was significantly up-regulated in the thimerosal treatment group, as if the cell was trying to get more cysteine in response to whatever the thimerosal was doing.

I'm not an expert. So I don't have like an experience level to say, well, okay, if I look at her you know, histochemistry as compared to other people in the field in general, to make a quality judgment on all of her figures. I have to say that I can't do that, but, from the cases that I have looked at. And I did look at all of the figures and so forth. I saw the differences that she referred to in the paper.

You know immunohistochemistry is a visual kind of

thing. It's not a number. So a lot of this falls in the category of, you could say, the art of doing this? So it's really a little subjective, in terms of was it good work, was it bad work, was it a clear result, was it less clear? I can't really judge art in that way, as well. But the differences were clear enough.

We also took on very recently a study of the levels of glutathione in the two strains of mice that Dr. Hornig studied. In fact, she sent us samples. Sent us samples of the SJL mice that were responsive to the thimerosal, and showed these changes, including the EAAT3; and then the C57 black mice brain samples.

We measured a couple of things. We measured the glutathione level, which we found that the thimerosal vulnerable ones had about 40 percent lower that was very clear; 40 percent lower levels of glutathione in the ones that she found to be more thimerosal sensitive.

At the same time, we measured the methionine synthase activity was with methyl B12 or hydroxy B12. Again we found the methionine synthase activity was lower by about 40 percent, consistent with a lower glutathione levels.

Those findings, made within the last month or six weeks, I would have to say suggest that there are strain differences in glutathione status and in methylation status, that make it reasonable that the thimerosal sensitivity

might be different between them. But this is different. We didn't measure the immunochemicals. We didn't do the behavioral studies and so forth. We just showed that the biochemistry is different between those.

Now I have to say also, and I will volunteer this, that the thimerosal treatment at 10 weeks did not affect those values. I just want to be clear. We measured with thimerosal treatment and without. But, in fact, they were lower in the SJL. But thimerosal levels were equally low and they remained low. What we see at 10 weeks after much earlier exposure is not clear. There are issues about when we measured it. But I'm just sort of volunteering, we know that there are strained differences in redox between those strains.

Q Now since you testified, have there been other animal models published that have tried to mimic the thimerosal vaccine doses that would support Dr. Hornig's conclusions?

A Since I testified, this has been more than two weeks or something like that. Yes, indeed, another study has come out. It's just, the way things are, there's a lot of interest in this, and now people are taking up the task of studying this. A paper that came out by Laurente, et al, came to my attention the day before yesterday I believe it was.

MR. WILLIAMS: Let me give you an exhibit number on it while we talk about it.

What is our next exhibit number?

SPECIAL MASTER HASTINGS: Number 11.

(The document referred to was marked for identification as Petitioner's Trial Exhibit 11.)

MR. MATANOSKI: Your Honor, I guess you haven't seen a copy of this, yet. But I heard this just came out, and I'm looking right at the bottom. It says 2007.

THE WITNESS: Maybe it was out but just not aware of it. It came to my attention not through PubMed, but through an email.

BY MR. WILLIAMS:

Q When did you first learn of this paper, that it had been published?

A Well, today is Thursday, and I think it was Monday night or Tuesday night. I believe it was Monday night. It was Monday night.

MR. MATANOSKI: Actually, I'm going to have to object at this point. I've been going with a lot of latitude on what's rebuttal and what isn't. This isn't rebuttal. This is available.

If he wanted to rely on this to prop up Mady Hornig's study, he could have done it then, when he was testifying. We're now at day 13 of the trial, and it's new

evidence that's been out there and it's coming in for the first time.

SPECIAL MASTER HASTINGS: Was it you or Dr. Deth that just said two minutes ago that this was published in the last two weeks? You asked him that and he said --

MR. WILLIAMS: I became aware of this.

SPECIAL MASTER HASTINGS: No, no, the question was, didn't you ask him -- I heard the words, published in the last two weeks.

BY MR. WILLIAMS:

Q Well, when was it published?

SPECIAL MASTER HASTINGS: Well, wait, you're dodging my question. Didn't you just ask him, has something been published? Did you use the words, published in the last two weeks?

MR. WILLIAMS: I may have; and if I did, I mis-spoke.

SPECIAL MASTER HASTINGS: Okay, all right.

MR. WILLIAMS: I apologize for that. I'm not trying to claim a different date than what appears on the paper.

SPECIAL MASTER HASTINGS: All right, I wouldn't recommend it. Do you have a response to Mr. Matanoski's objection?

MR. WILLIAMS: Well, I tell you what, because

this deals with toxicology, we can take this up when we do our rebuttal on toxicology in July.

MR. MATANOSKI: Not unless Dr. Clarkson and Dr. Magos talk about it.

MR. WILLIAMS: I'm sorry, I didn't hear you.

MR. MATANOSKI: Not unless Dr. Clarkson and Dr. Magos talk about. What I'll do, Your Honor, is this. I'll reserve my objection. I'll allow the question to go forward with that reserved objection.

Dr. Johnson, if he comes back tomorrow, if he wants to address it, we'll address it and then decide whether or not to withdraw that objection. So that way, you'll have the testimony in front of you. We can all hear it. We can see what we're going to do with it after that.

SPECIAL MASTER HASTINGS: All right, then go ahead, Mr. Williams.

MR. WILLIAMS: Let me just say, I think this is an issue that's going to come up again and again. Because there is so much new science being published as this proceeding goes forward. From the Petitioner's point of view, you believe we should have all the science available, even if it is brand new.

SPECIAL MASTER VOWELL: If this were new, I might agree with you. But it's not new.

MR. WILLIAMS: It's new to us.

SPECIAL MASTER VOWELL: What we're trying to emphasize is that there's been a very lengthy ramp-up to trial here. You all had this opportunity to find these things. Having them sprung on the Court at the last minute is not helpful.

MR. WILLIAMS: I'm sorry.

BY MR. WILLIAMS:

Q Just briefly then, Dr. Deth, explain why you think this paper supports your general opinion.

MR MATANOSKI: Well, actually, I think it has to be in support of the criticism of Dr. Hornig, as this is rebuttal.

Q Does it help you to reinforce what you have relied on from Dr. Hornig's paper?

A I think I should probably frame what I relied on from Dr. Hornig's study in the first place, and then just reflect on that.

In Dr. Hornig's study, as we recognize, it was an attempt to replicate the developmental timing of the delivery of thimerosal and thorganic mercury in hopefully a relevant model system; two strains of mice that have a background of an auto-immune prone nature to them.

At the time, I provided my expert opinion here, which was before Berman's paper was published, I didn't have the counter finding that they had that that time; that paper has shown that there were neurological effects, as well as

effects as EAAT3, which I found particularly connected to my line of research and my line of opinion here.

Now this study -- which in fact, Dr. Hornig was not aware of. When I saw this on Monday night, I sent an email to Dr. Hornig and said, are you aware of this paper? So as invested as she is in this field, you know, the paper apparently was published originally in 2007. It escaped many people's attention.

In any case, this paper shows, as the title describes, toxic effects that were quite striking, in a different species. In this case, there weren't two strains of the animals. But in this case, the hamsters that they used were one strain, and they were treated or not treated with thimerosal; and then certain brain end points including size of the brain with different brain structures, as well as the vitality and neuro degeneration status of different types of neurons in different locations, which were found to be affected by thimerosal.

So these were quite striking, indicating that again the develop mentally matched delivery of the thimerosal in these animals caused neurological damage.

Q Now one general criticism that I think all four of the defense experts made of your work is that you can't extrapolate from in vitro studies to living human beings. You know, what is your response to that?

A This is an easy general criticism. But it strikingly, it does not apply in this case. To the contrary, the work that we initiated in vitro, in culture neuronal cells. Again, Waly's paper that came out, more or less simultaneous with the IOM hearings, the open hearings, pointed to methionine synthase and to methylation as an event that is exquisitely sensitive to thimerosal in vitro. That's all it was at that time.

At that time, well, actually, while that paper was in review and in press, I attended a conference at which a clinician, where Dr. James Neubrander described his experience administering methyl B12, methylcobalamin to an autistic patient; and you know, the mother coming back to his office excited after 10 days, two weeks later, to say, oh, her son was so much improved. It was just like her son had had a miraculous change.

So in any case Dr. Neubrander related methyl B12 had an effect in autism. From that time, we took on a study methyl B12 at that time. But from his clinical experienced, combined with our in vitro work, we then went back to the in vitro system to say, well, methionine synthase methyl 12. What could be special about that? Why would this methyl B12 be any different than the regular B12?

That lead us successfully, as I said before, to understand that neuromal B12 had a special B12 requirement;

and that it needs to be glutathione dependent synthesis of methyl B12, and that redox interferes with that, et cetera, et cetera.

So this really is an extraordinary example, looking back at it, of how an initial in vitro finding can be coupled with clinical experience, and a back and forth can occur between clinical experience and the in vitro opportunities to study that, which currently cannot be studied in humans; and along the way, as it turned out, Dr. Jill James undertook her studies of sulphur metabolism; and she also found that the administration of methyl B12 normalized these metabolites in autistic children.

Then more recently, there was an article thats in press discussing findings that cognitive abilities are improved by methyl B12 and folic acid or folinic acid treatment. So in the interest of finding correct answers to the issue here, these studies converge to show that in vitro data, and the results that it can produce, are invaluable in understanding the mechanisms that contribute to the in vivo condition; and also to finding treatments that can reserve the in vivo condition, that one couldn't ask for a more satisfying the relationship and a more utilitarian role for in vitro studies than that.

Q Now you've referred to some unpublished work of Dr. James. Is there a lot of scientific work going on

that's headed towards publication, as we sit here today, that are relevant to the issues these Special Masters have to decide?

A I think that's obviously well beyond my testimony, and even well beyond the area of my personal interest in thiol issues and redox issues.

But even in the thiol redox, that represents a hypothesis; and a hypothesis that was introduced now, let's say, three to four year ago; and as such, this can be tested and it is being tested by these individuals that are carrying out research. Some of it is clinical. Some of which is biochemical.

Then that, coupled with the dramatic need to find answers here, when you have at least a reasonable hypothesis to put forth that's concrete enough to be tested, that's an important starting point, and it has attracted a number of researchers. Again the issue of autism being as important as it is, not only to the public health, but to the families that are involved.

Certainly, it is a driver for a greatly increasing amount of research efforts and publications at present, and I'm sure that will continue.

Q Specifically, not just on autism, but on the potential relation of inorganic mercury to autism.

A That's exactly correct; although I'm trying to

think of a Greek analogy where you can come too close to something. Was it from Ichtheus or who was it?

Q Icarus?

A Icarus and United and so forth -- it turns out that the issue being as controversial as it is and we're gathering here to try to resolve some of that controversy. It has, in many cases, been a barrier; not only a financial barrier for the lack of funding, but for important issues of, will I be tainted by taking on a research into such a controversial area?

This is the reality of doing research. It's a question that I'm sure that different people have pondered. But I know this first hand. So in any case, I suspect we would see even more research into the mercury connection, if it weren't for the fact that this is dangerous territory to some

MR. WILLIAMS: Okay, thank you; that's all I have.

SPECIAL MASTER HASTINGS: Do you have any cross examination?

MR. MATANOSKI: I do. I think I might be able to finish it without having a break. We're getting near the morning break time.

SPECIAL MASTER HASTINGS: Do you want to go ahead and try? Why don't we take our morning break?

(Laughter.)

SPECIAL MASTER HASTINGS: It's nearly 10:45. Let's go until 11:00.

MR. MATANOSKI: Thank you, sir.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: Please be seated. We're ready to go back on the record. Dr. Deth is still on the witness stand; and Mr. Matanoski, go ahead with your cross.

MR. MATANOSKI: Thank you.

CROSS EXAMINATION

BY MR. MATANOSKI:

Q Good morning and welcome back, Doctor.

A Thank you.

Q I first want to make sure I understand your hypothesis that you've come back now to talk about. I want to put up your slide 7 that you've provided in your direct testimony, and make sure I understand you hypothesis here.

You have genetic risk factors, neuroinflammation, all impacting on the redox capacity. Is that right? They are contributing, along with the heavy metals, to create a situation of oxidative stress? Is that it, in a simplistic form?

A That is correct, yes.

Q Then the oxidative stress impacts methylation and

more neuronal synchronization on the one hand?

A Which I have chosen a couple of things to highlight here, out of too many to enumerate.

Q Okay, but it affects many things.

A That's correct.

Q Then the other thing that's important for your hypothesis is that it also creates neuronal and glial degeneration. Is that right?

A Neuronal degeneration -- here, I was referring to the relationship that it has to diseases like Parkinson's and Alzheimer's. The slide is not explicitly I guess an autism slide. But otherwise, neurodegenerative diseases such as Parkinson's and so forth, certainly the oxidative stress is an important contributor to that.

Glial cells don't necessarily degenerate. They have glioses, for example, or in the case of activation of microglia, I suppose the term degeneration might not apply to those outcomes equal to neuronal degeneration. Again had the neurodegenerative diseases that I meant to include in that arm.

Q Okay. So then are you saying that the neurodegenerative diseases are caused by heavy metals since that's part of this process as you described it?

A They can be I suppose. The clearest examples would be even for clearer for xenobiotics, but none of us

have the idea that there's a theory there, for example, for aluminum, and Alzheimer's is certainly one of the theories and heavy metals in Parkinson's as well. But exposure to paraquat in Parkinson's would fall in the xenobiotic category.

Q So is this presented as slide 7 to the Court, an autism case? This mechanism then is not specific to autism. Is that what you're telling me?

A No, in fact, it does encompass other things, other than autism.

Q So your process, as you described it, is not specific?

A Excuse me?

Q It's not specific to disease.

A I think you made a jump somehow here. Between saying slide this specific to the fact that --

Q You presented the slide in a case about autism.

A Yes.

Q It describes your process.

A My process?

Q The mechanism of how autism is caused by heavy metals.

A Yes.

Q And you're telling me that this is not specific necessarily to autism.

A I suppose I could counter by saying the brain is not specific to autism. So events that affect the brain, but might not be occurring with the same temporal or developmental circumstances as autism that might occur late in life; for example, in the case of more degenerative diseases, might logically involve the same critical factors for brain metabolism. So those factors are shared by different diseases; of which autism is one, but not the only one.

Q So this hypothetical process doesn't necessarily apply just to autism. It could apply to many different things.

A I regret your choice of the term hypothetical process. The metabolis of the brain that introduce vulnerability apply to many diseases affecting the brain.

Q The process you've described is not specific to autism then. The process that you've laid out to the Court is not specific to autism.

A The elements I layed out have to do with thimerosal as a causative agent. And the timeframe and the prevalence of its administration and its particular properties that of inorganic mercury in the developmental stage, those things are specific to autism.

Q Acting through the mechanism for oxidative stress under your hypothesis, correct?

A Correct.

Q That mechanism is not specific to autism. Is that correct?

A The mechanism can be important at other life stages in other diseases.

Q In fact, you, yourself, have attributed obesity to thimerosal, correct?

A No, I believe, as we discussed in my cross examination, that I brought to the attention of the people that I gave several lectures to the fact that the risk genes identified in autism have also been identified as risk genes for obesity.

And to me, it raised the interesting possibility, and I still regard it as such, the interesting possibility or hypothesis that individuals who are affected by oxidative stress but carry other genetic risk factors or experience other genetic risk factors of which one could consider overeating, for example, a risk factor that by itself might not trigger obesity but in the presence of oxidative stress might, and I emphasize might, lead to consequences. So this is a hypothesis that I've entertained.

Q Doctor, haven't you publicly stated that you believe that it's at least possible that thimerosal vaccines have led to an epidemic of obesity in children?

MR. WILLIAMS: I object on the grounds that he's

going off in other directions that we dealt with on the rebuttal. This cross may have been appropriate two weeks ago. But it's not appropriate today.

MR. MATANOSKI: I'm trying to understand Dr. Deth's theory. He's been talking about it this morning. I'm now hearing that it's not specific. I was trying to narrow it down to autism. Again, that could be Parkinson's, later diseases in life. I'm just making a point that his theory, as he's trying to defend it here in rebuttal, is not specific to the injury that you have before you.

SPECIAL MASTER HASTINGS: Well, I understand your point. But you're not addressing Mr. Williams' observations just now; that this doesn't seem to have anything to do with what he testified to this morning in rebuttal.

MR. MATANOSKI: I would simply observe that to the extent he was trying to defend his mechanism, that it would. However, Your Honor, I will withdraw it.

SPECIAL MASTER HASTINGS: All right.

BY MR. MATANOSKI:

Q Glutathione is the primary inter-cellular anti-oxidant. Isn't that correct?

A I think that's correct.

Q So it's critical, at least in your mechanism, to the role of oxidative stress. It's presence is critical to it, isn't it?

A It's a major factor in determining the presence or absence of oxidative stress. That's correct.

Q And Dr. Jones testified that your body has abundant glutathione available, correct?

A If that's correct.

Q You did listen to his testimony,

A I'm sure he did. I'm just wondering about the fact that I don't have verbatim knowledge of what he said. But I gather, that's a general statement about what he said.

Q Well, you were responding to his criticisms of your work. You did listen to his testimony; did you not?

A It was indicated that there is a lot of glutathione in the body. That's correct.

Q You don't gain-say that, do you?

A Gain-say, meaning?

Q You don't contradict that scientific fact, do you?

A No, I don't.

Q In fact, wasn't the thrust of his testimony to give context to this Court about the amount of glutathione in your body versus the amount of glutathione that would be needed to metabolize mercury that the body received? Isn't that correct?

A If you could restate the beginning of your question, you said that wasn't the intent. Is that what you

said?

Q Wasn't the thrust of part of Dr. Jones' testimony that the amount of glutathione in the body can abundantly take care of the amount -- to give context to the relative amount of glutathione, versus the amount that would be needed to process the mercury that was received through vaccines? Isn't that right?

A My understanding of his testimony, as I heard it and read it, was that mercury would be overwhelmed by that large amount of glutathione and, therefore, it should be, I suppose, innocuous, or otherwise non-toxic, correct.

Q That's what I understood, too.

A Of course, this would be a contradiction to our understanding of what mercury is. But that's the point that he made.

Q To your understanding of what mercury is -- is that correct?

A Mercury is generally regarded as both a toxin and a neuro toxin, despite very high concentrations of glutathione that we have.

Q And the glutathione levels in the body are abundant, correct?

A They are abundant.

Q Dr. Deth, how many articles have you published on glutathione?

A On glutathione, I guess one, which was the review article -- in fact, the Waly article showed these effects in the first place. We weren't aware of the critical role of glutathione at that time.

Q So that can be addressed.

A So the other articles that are already out, I think there's only just the others that are in press.

Q So you have your one article, that was a review article?

A That's right.

Q Then the others are in press.

A That's correct.

Q Do you know how many articles Dr. Jones has written on that topic?

A Abundant, I suspect.

Q And oxidative stress is key to your mechanism, correct?

A It is.

Q How many articles have you published on oxidative stress?

A I suppose it's that same one, with regard to already published articles; that's correct.

Q So it's looking at the work of other individuals, a review article?

A I suppose we've done the research that I've

presented here, with direct participation in measurement of glutathione --

Q This is the unpublished work that you presented.

A The unpublished, direct research that we've done.

Q I asked you about articles.

A You asked about what?

Q I asked you about articles that you've published.

A Fine, I said that I've only published one.

Q The review paper.

A That's correct.

Q That was 2008.

A Correct.

Q Do you know how many articles that Dr. Roberts has published on oxidative stress?

A Again, I assume it's a large number. Actually, I believe that's been the nature of his focus throughout his academic career. I don't know that number. Perhaps you can help me.

Q You mentioned the 2004 article by Waly, and I believe you were one of the co-authors in that study. Is that right?

A Yes, I was the senior author of that.

Q Okay, I'm sorry; the senior author in that study -- now you didn't get that published at the first journal you went to, did you?

A No, that was submitted first to Nature --
Q And they rejected it.
A That's correct.
Q And then you didn't get it published at the second journal that you went to.
A That's correct.
Q They rejected it. It was the third journal that you went to?
A Actually, this is the fourth. Actually, I submitted it to --
MR. WILLIAMS: I want to renew my objection. This has nothing to do with what we talked about this morning. This has to do with general topics.
MR. MATANOSKI: I believe he was talking about his 2004 Waly article, and trying to defend his previous opinion in this case.
SPECIAL MASTER HASTINGS: Well, the article was discussed; but nothing about issues of how many publishers it went to. So why don't you move on?
MR. MATANOSKI: I would submit, Your Honor, that it goes to what weight you should give to the evidence that he's countering with now.
SPECIAL MASTER HASTINGS: Well, of course, he discussed Waly in tremendous length in his initial testimony; and this is clearly the type of question that

could have been asked on cross.

MR. MATANOSKI: Very well, Your Honor.

BY MR. MATANOSKI:

Q You, in your lab and experiment, have found that a dose responsive effect for thimerosal at the .1 nanomolar range. Is that right?

A It stated that subnanomolar concentrations cause significant effects.

Q That was .1 nanomolar, right -- subnanomolar, then?

A Correct.

Q And that was published in 2004. Is that right?

A I believe that's correct.

Q Since that time, that that was tested, you were defending yourself this morning, saying that you were being criticized because you were the only one who had a seen a .1 nanomolar effect. That was published in 2004. In 2005, Dr. James also tried to do a dose response effect, correct?

A No --

Q PML 007?

A Excuse me?

Q It was Petitioner's Master List, 007. Wasn't her effect --

A Did she measure the same thing that we measured?

Q She was trying to get a dose response effect to

thimerosal.

A What was she measuring? I think I know the answer, and I'm just saying that you're not asking about whether did we measure the same things. I believe she measured toxic effects with a cell death end point. I don't believe she measured in SY5Y cells, phospholipid methylation.

Q So she used different cells and that's why she had different results?

A No, she used the same cells. In some cases, she used I believe a glial cell lines and the SY5Y cells but was looking at the toxic effects on cell death.

Q When she reported it, it was at four orders of magnitude greater to get a dose response, isn't that right?

A In other words, the concentration needed to kill the cells was --

Q To get a dose response. Four orders of magnitude.

A To get a dose response, killing the cells?

Q Yes.

A I believe it was between one and 10 micromolar. So that would be, again, to kill the cells, you need perhaps at least 1,000, maybe 10,000 times higher. That's correct.

Q So four to five orders of magnitude?

A She also had a 15 percent FBS concentration.

These are details. There were some experimental details that were I'll say different between the two labs. But the end issue of the large difference between the amounts necessary to kill cells and to interrupt their function remains.

Q The experimental details, that's what Dr. Jones was dealing with, that the experimental details can affect the results that one obtains on this dose response relationship, correct?

A The details, I suppose the belies the importance of experimental conditions. We used 10 percent FBS. She used 15 percent FBS. The FBS is a source of growth factors that can stimulate the cysteine uptake through EAAT3 and as a result can increase the cysteine uptake, making the vulnerability to heavy metal toxicity less.

So at least part of that 10,000-fold difference could be explained on the basis of the fact that the availability of a cysteine resource was greater in her conditions. But the major reason is the fact that she's measuring the death of cells whereas we were measuring I suppose processes that were more functional and were certainly more I would say subtle by comparison to cell deaths.

Q And you just said that the experimental conditions alter the amount necessary to create the dose

response, is that correct?

A I noted these experimental differences. We haven't made an experiment out of testing those factors.

Q Humphrey in 2005, and this is Petitioner's Master List 008, the amount necessary to create the effect there in vitro was 2,500 to 5,000 nanomolar, correct? That is again four orders of magnitude --

A My memory --

SPECIAL MASTER HASTINGS: Gentlemen, let's have mercy on the court reporter here. We're getting lots of time when both of you are talking at the same time, and I can't imagine how we'll ever get a transcript of this. So please, let's try to go one at a time. Go ahead and ask your question again, Mr. Matanoski.

MR. MATANOSKI: Thank you.

BY MR. MATANOSKI:

Q In the Humphrey article, this again was after your work in 2004, it required four orders of magnitude greater to get the effect.

A I'm afraid the Humphrey article, you'll have to refresh my memory. By the first name, I don't identify articles well enough by first name to know which one you're referring to.

Q Very well, Herdman, are you familiar with that, another article to test the effect of thimerosal on cell

culture?

A If I had the --

Q PML 024, you're not familiar with that?

A PML 024?

Q I'm sorry, Petitioner's Master List 024. I was just doing that for the benefit of the record.

MR. WILLIAMS: I would request that if you're going to ask the witness about an article, that he be provided a copy, as a courtesy.

SPECIAL MASTER HASTINGS: That seems reasonable. Well, why don't you ask then? Then see what the question is, and see if you need the article.

BY MR. MATANOSKI:

Q I'll just sum up. Since your article was published in 2004, six additional researchers have come out and attempted to determine what amount of thimerosal is necessary to get a threshold effect, a dose response effect. They were all four of magnitude greater than you. Isn't that correct; greater than your 2004 article?

A My understanding is that no one has measured what we measured. We haven't measured cell deaths. They have measured cell deaths, and perhaps other end points of pre-apoptotic or other end points.

So my thinking is, no one has measured what we measured in the cells that we measured, the way we measured.

So there is no comparison. It's like apples and truck.

Q So in the four years since you've put that result out there about thimerosal, six researchers have gone around and they've looked. Your results have been out there, addressing the question in the fashion that you did, in terms of inhibition; and they used a different approach to measure the effects of thimerosal in cell culture. They did not adopt your approach to measuring the effect, correct?

A At the risk of self-flattery, there's one or two or a few key things that cause and contribute to autism. If you're examining those things and measuring those things, you might find a differential sensitivity to the factors that contribute to autism. Death of cells is not a key feature of autism. Therefore, the things that we measure have a unique likelihood of reflecting critical events, and they may therefore have a unique likelihood of being more potently affected by the same factors.

Q So you're the only one looking at this, looking at this particular effect on cells?

A I'm the only one. In the system, in the human neuronal cells, I believe we are the only ones who have measured methylation status and redox status in human neuronal cells.

Q We've talked about Dr. James' work at length this morning. Dr. James, when she went to look at it after you'd

done your work, she looked at it in a different fashion. She didn't even adopt your approach. Is that right?

A She measured the cell deaths, is that what you mean?

Q I believe so; and she needed four as a magnitude greater than what you had.

A To kill cells -- I'm thrilled with that, and I'm sure every parent of an autistic child is thrilled that it takes four orders of magnitude more to kill the cells. However, I otherwise base my testimony on the fact that loss of function in neurons in the human brain can occur with much more restricted levels of inorganic mercury.

Q The other researchers haven't taken up that challenge. They haven't seemed to try to duplicate your line of research. Even though they're looking at thimerosal, they aren't looking at it to do the same effects that you are. Is that right?

A People have different thrusts or research interests and/or abilities and systems. Dr. James, for example, that you seem to be drawing attention to here has drawn her attention and admirably so toward the clinical status of children with autism, measuring the very same thiometabolites in ways that she's able to and then moving on to look at the effective therapeutic interventions. So thankfully we're all not doing the same thing, but they are

complimentary to each other.

Q Now you mentioned this morning when you were given an article by Arne Holmgren called Inhibition of the Human Thioredoxin System, you discussed this this morning at some length. You mentioned in fact that you had a conversation with Dr. Holmgren six months before this article was published. Is that right?

A I think I mentioned we had an email exchange.

Q An email exchange, very well, six months before this article came out.

A That's my recollection, yes.

Q And you discussed your work with him?

A I did.

Q Was that the first time he was aware of your work?

A To my knowledge, it seemed to be.

Q I was doing a quick look at his sources, in terms of his references in this article, and I don't see your work referenced there.

A In confirming our lack of mutual knowledge of each other's work, that's correct.

Q So even though you told him about it, he didn't see fit to really include it as important at least in the experiment that he was doing on thioredoxin?

A An unflattering interpretation, but the fact is

that when I talked with him, he indicated that he had an article that was already submitted, and I suppose in the absence of knowing me, but he's not necessarily, although he could quote our work, we don't study thioredoxin.

Q Yes. In fact, I don't remember you citing thioredoxins at all in your expert report.

A Which I have to say I'm thrilled to have this improved understanding of thioredoxin as a result of this proceeding, because from Dr. Jones and now Dr. Holmgren and the occasion of this hearing, these proceedings here, my attention on thioredoxin has now improved, although I did, as you recall, suppose that if thioredoxin or glutaredoxin were the likely intimate targets of inorganic mercury.

Q So your understanding of this topic is progressing as this litigation goes on. Is that a fair characterization?

A This paper has improved my understanding. That's correct.

Q And this paper came to your attention this past week.

A That's correct.

Q When counsel gave it to you.

A No, in fact, it was a sequence of events. I discovered it and gave it to counsel.

Q I see, and Dr. Jones, as was pointed out this

morning, his work is mentioned several in this thioredoxin article, correct?

A Yes, it is.

Q And you listened to his testimony, correct?

A Correct.

Q And you heard him explain in response to counsel, that this does not impact at all on the question before the Court about thimerosal and its effect on oxidative stress or sulfur metabolism, correct?

A I think he used words to that effect. Although I believe he used them incorrectly. I think he was somehow taken aback by the fact that his work provided strong relevant effects of evidence in favor of a likely target here, as provided by this paper.

So my opinion, upon hearing him and the tone and I guess the nature of the exchange, was that he was somewhat surprised by the fact that his own work seemed to support an important factor in the causation.

Q At least as far as counsel was postulating it, it was an important factor.

A Yes, I mean, from what I thought --

Q Dr. Jones.

A -- his remark was, his remark and his response to say that it didn't, in his opinion, have a bearing, was I believe an attempt to isolate himself from the possibility

that the thioredoxin would have; that because he was in the awkward position of being the expert witness, whose own research had an important positive relationship to the causation theory being evaluated here.

Q His conclusion under oath was that it did not have any effect on the issue before the Court. It did not change it one way. Isn't that correct?

A That was the tone; that was the sense that I gathered from his comments. Whether you're asking me explicitly, did he say those words, I don't recall whether he said those words.

Q And thioredoxin, how many articles have you published on thioredoxin?

A I haven't published any articles on thioredoxin.

Q In fact, you weren't even considering it in your calculations, at least as far as your written report or your testimony two weeks ago, as part of the equation on how thimerosal causes autism. Is that correct?

A I put my arms out like this, and I sort of tried to recreate my description of why inorganic mercury -- the released inside the brain preferentially from ethyl mercury compared to methyl might have toxic effects on thiol metabolism. I indicated its likely targets was proteins in which cysteine residues, like number 32 and 35, in the thioredoxin would, in effect, should be considered as the

target.

Because I was trying to make it clear that glutathione interactions were not the point here. Because interactions with proteins like thioredoxin was the point. I alluded to that.

Q You actually used the term thioredoxins?

A I might have said glutaredoxin. I'd have to go back to see what I said, that Dr. Holmgren in his paper points out. These two proteins, they share structural features in an intimate way.

Q And you acknowledge that Dr. Jones, in contrast to yourself, has published on thioredoxins.

A Oh, I acknowledge that, and I'd be happy to reiterate it.

Q Now I asked you a question before when you were first up here about Jill James and the strength of her work at least as far as supporting your hypothesis. You indicated that her work was the strongest support for your hypothesis. Do you still hold to that?

A In broad terms, yes.

Q We went through some slides this morning, and I just wanted to go thorough and verify. Slide 28 that you went through, that was never published, is that right, the material on that?

A That's correct.

Q And slide 34, the material on that was never published, either.

A Correct.

Q Now you said that you really had not published this because you wanted to be more complete with your understanding, is that right?

A In terms, yes, we wanted to have what would be to an external reviewer or audience. It would be a more complete view of the thimerosal. But it's not about thimerosal. As important as that is in this proceeding, it's really about understanding the role of methionine synthase in neuronal cells and neuronal tissues. So we wanted to have a more both satisfying to ourselves but also to reviewers, a more complete picture of these events.

Q So the picture is not complete at this point.

A A picture of this nature is never complete. However, I do believe with our recent recognition of the inhibition of the cysteine uptake, which accounts for the large decrease in the amount of glutathione -- the decrease being 40 percent -- we know that it's not just a shift in redox state, where all that 40 percent just is now oxidized.

That's not the case. We had to otherwise understand why the amount of glutathione would be quantitatively as so much lower. Now we realize that it's because the uptake of cysteine is reduced proportionately.

So that is a major improvement in our understanding of the overall system. Then, to my mind, it allows us now to go ahead and present and cohesive, coherent description.

Q But just this morning you were saying that you're still waiting for the story to become complete, and that's why you hadn't published it. You're going to get it ready for publication. In a couple of months maybe it will be published. But at this point, the story is not complete?

A It will be submitted for publication. I trust what you're talking about; what are the factors that limit not only the choice to publish, but of course the time to do that writing and teaching and other commitments and obligations.

They play a role. So it's not exclusively a matter of completing the story. But that was the important thing, to be able to have an adequately comprehensive body of data and knowledge about the system.

Q But you feel it's adequate enough, in your view, to present to the Court.

A That's right, recognizing that science, in general, is going some place; and now we have made the significant advance, and enough coherence exists to update, if you will, our earlier paper; and convince other people, as well as ourselves, that this explains the mechanism of the lower methionine synthase activity that we earlier

published. Yes, I believe it adds that point.

Q You mentioned a moment ago a 40 percent reduction in glutathione and its relative importance in the question before the Court.

A Yes.

Q I believe you had referenced earlier the work with Jill James with respect to that finding in autistic individuals.

A That's correct.

Q Did you hear the testimony of Dr. Aposhian, when he was here? I believe you were in the courtroom on the first day of trial.

A I was here for the second day of trial.

Q You didn't hear his testimony then.

A I didn't hear the first day of testimony.

MR. MATANOSKI: Could we play Dr. Aposhian's testimony with respect to Dr. James' work with glutathione?

(Audio of Dr. Aposhian's testimony from May 20, 2008, played as follows.)

"Q Does glutathione only protect against mercury, or does it protect and aid in detoxifying other substances?

A A concentration of glutathione in your liver cells is 10 millimolar, and 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; there are not only metals, but many other agents. Glutathione is one the major endogenous detoxifying agents that we have. 10 millimolar 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, a hypothetical -- if your levels of glutathione are so low that you cannot detect or 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. Now what you must say is that 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 glutathione. She did not do brain glutathione. She did red cell. No, she didn't even do red cell glutathione. She studied plasma glutathione.

As I and everyone else have told her, plasma does not have a high level of glutathione. Most glutathione is an inter-cellular compound. Very little glutathione is found extracellularly. I don't know whether that helps you

or not.

Q No, it helps me."

(Audio of Dr. Aposhian's testimony from May 20, 2008, concluded.)

BY MR. MATANOSKI:

Q In fact, her work that shows the 40 percent reduction in autistic individuals, the toxicologist that appeared for the Petitioners said that that can be given very little value in determining what is going on with the amount of glutathione and what effect it has on the body. Isn't that right?

A Dr. Jones, I think said that. Is that what you're saying?

Q Dr. Aposhian -- that was Dr. Aposhian's testimony you were hearing. He was discussing Dr. James' work with respect to glutathione.

A Did he say that her work could be given minimal value?

Q He said she is measuring it in plasma; and as he said, he and everyone else, as he put it, told her that that that was not the proper way to measure for the glutathione.

A He did say it wasn't the proper way; measuring in the plasma is measuring in the plasma. Measuring in cells they're two different things.

Certainly, a diagnostic test of plasma levels is

not an unusual thing to measure. It's not wrong, and she measured it the right way. It tells us certain information. It tells us what the plasma level of glutathione is. It doesn't tell us what the inter-cellular concentration is. It doesn't tell us what the brain concentration is.

But it does tell us what the plasma level is in a comparison among individuals who are fasting and otherwise it is drawn early in the morning; and therefore, has certain attempts to normalize the fluctuations. That has to be given the weight that the data itself merits.

In this case, the considerable differences, not only in glutathione, but every saved one that was measured shows pervasive abnormalities between these two test groups and the subsequent study confirmed that autism is associated with a major difference in plasma level. Again, you have to just understand that it's plasma level. It's not wrong. It's plasma.

Q So you continue to maintain that Dr. James' work is the strongest evidence for your --

A Yes. I certainly do.

Q You discussed Mady Hornig's paper this morning, and you mentioned the criticism from Dr. Berman. But I didn't hear you comment on that. What comments do you have on the criticism from Dr. Berman? Have you read it?

A I have read Dr. Berman's paper, which did not

find, did not confirm, Mady Hornig's paper. This is a study in mice, measuring what they measured. They are important insofar as that represents a model system of thimerosal toxicity, and especially on neural end points.

As far as Berman's failure to replicate, I don't really have a cogent explanation for why it failed. There are noticeable differences in the way the animals were in the same litter; both treated and untreated. This may or may not have been a factor. I think there are issues to be sorted out between those two labs; and I suppose the paper on the hamsters that we mentioned this morning add an additional element, on the face of it, that would strongly favor Hornig's findings.

But those people have to work out those differences. Science is such that as long as people aren't lying about what they did, as long as they measured things reasonably in a common manner and by experimental methods, it can be explained and replicated. That they should be able to figure out why a difference occurred.

Q Dr. Berman used a quite considerably higher dose of thimerosal in the animals he treated?

A He did as part of the study using an extraordinary high dose.

Q And he did not get any effect; is that correct?

A That's my recollection, as well.

Q You said that this paper that you put out this morning, you believe contributes to the discussion as to which lab should be followed; whether it's Dr. Hornig's or Dr. Berman's?

A You've added some specifics there; which one should be followed. I think it's a difference species. I, myself, I find myself this morning wondering whether hamsters -- because of the extent of the damage and neurologic or actually neuro anatomic effects that they observed in that hamster study, I said gee, maybe those certain golden hamsters that they used are somehow more vulnerable. Because quite frankly, it goes beyond Hornig's findings, in terms of the extent of the effect.

So I wondered whether or not their redox status, as a species being different than mice, might not make them more vulnerable. That's just a thought on my part.

So my take of this other study is that it adds something, but it still needs to be understood itself, the same as the other mouse studies do.

Q And this came out in 2007, and really, this was published in the Annuals of the Faculty of Medicine of Lima. Are you very familiar with that journal?

A I'm not familiar with that journal.

Q Had you ever heard of it before?

A No.

Q Now you presented a chart in your slides that gave you the whole hypothesis. In your slide it was chart 41. That sort of summed up your hypothesis. That was similar to the chart on the paper you referred to this morning; you review paper published in 2008.

I think if we could put that up, it will show that the review paper you published I think was -- I've got to figure that out. It was PML 563, on page eight of that. The other is your slide from your testimony. It's slide 41, the last slide.

I think we've discussed that neuralinflammation was added to this, at least for the slide. But otherwise, it's the same theory that you published.

A It certainly is the same theory, yes.

Q I believe you were saying that neuroinflammation has always been part of this theory.

A The pathologic term of inflammation is not a bio chemical term. Oxidative stress is not a pathologic term. It's more of biochemical event. The two are closely related, and I wanted to make sure that for purposes of this Court proceeding, that the terms in relationship to each other were clear.

Q In your discussion this morning of your review paper which laid out the hypothesis, you pointed out that you had discussed part of the Pardo paper in that and

neuroinflammation. Is that right?

A That's correct.

Q Now in the conclusion of that 2008 paper, you summed up, and we'll pull that up again. This is PML 563. This is on page nine of that. If you could pull up the highlighted section. It's your description overall of what you observed in that paper.

You said specifically that the validity of any hypothesis requires that it accounts for relevant, previously disparate observations. You go on to say that you think that your theory accounts for most of those. But it doesn't explicitly account for all of them.

Now what you say in sort of summing this up is, your theory, "may serve as a useful starting point that can be critically tested and accordingly revised and even discarded," and that's where we stand today, correct? This came out in 2008.

A Are you saying that it can be critically tested. First of all, it's a useful starting point. It can be critically tested, and can be revised or discarded.

Q And that's where we stand today with your hypothesis, correct?

A It's kind of a general statement about the hypothesis and the flow of science.

Q This is statement about your hypothesis.

A That's correct, which is an example of a hypothesis in the flow of science, where there are things that we don't know. There could be revelations that research will uncover next week, next month, and I would revise my understanding, if I have to. But at this point in time, I've done my best to integrate and to describe the relevance of these events as they relate to autism.

Q And it awaits critical testing at this point.

A Further critical testing.

Q Thank you.

A Thank you.

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

MR. WILLIAMS: Yes, I have just a couple of points.

REDIRECT EXAMINATION

BY MR. WILLIAMS:

Q First, quickly on the hamster paper, do you know whether that journal is listed in PubMed?

A I assume it's not. I but haven't searched for it.

Q You haven't checked; and do you know that journal is actually a Spanish-only journal?

A I would presume it is a Spanish language.

Q And do you know when the English translation

became available?

A I don't know that. This article just came to my attention. I don't know the origin or the history of that article; except that I understand that the journal represent the medical organization in Peru, and is considered, I guess, sort of a JAMA, as being a Journal of the American Medical Association. But it somehow has a standing in Peru. But I'm not familiar with its lineage that much.

Q Then on your theory, your hypothesis as the DOJ calls it, do you believe that it is biologically plausible?

A I have no doubt that it is biologically plausible.

Q And do you believe that it represents a logical sequence of cause and effect?

A I do, and that belief is based upon a number of factors; not only in relying on my own in vitro work model or our own brain work, but also the diagnostic testing and clinical testing and the therapeutic treatments that improve autism; all those things combined feed into my opinion.

Q As far as you know, is it consistent with all published data so far?

A All published data so far.

Q Is there any publication that would contradict part of this logical sequence that you've laid out?

A Not that I'm aware of, no.

MR. WILLIAMS: Okay, thank you.

SPECIAL MASTER HASTINGS: Is there anything further?

MR. MATANOSKI: Yes, sir.

RECROSS EXAMINATION

BY MR. MATANOSKI:

Q When you write for the medical community. Again, in 2008, you say that your theory can't account for everything. You said it can't account for autism observations, such as abnormalities in brain size, myelination patterns, or serotonin levels. Isn't that correct?

A I wrote that, and I would be happy, since you bring it up, to indicate that there are connections with those things. But I didn't think it arose to the level of certainty that I could expand on them in that paper; for example, myelination. Myelination involves oligodendrocytes functions and the lineage of oligodendrocytes is regulated by redox status. I believe there was testimony to that effect by Dr. Nobles, for example.

Moreover, myelination involves methylation of myelin-basic protein. So the methylation of that that represents could be subject to influences of the redox. Moreover, brain size reflects the result of growth factors, that signal through PI3 kinase, like insulin-like growth

factor, that determines brain size. We have shown that insulin-like growth factors though PI3 kinase regulates these pathways.

So it's not like there aren't elements of this hypothesis or this area of science that couldn't relate to those things. The question is whether those areas are fully mature in terms of the studies that would allow a forthright and more definitive statement about that. But there are ways in which they easily could be related to this.

Q All right, and when you're writing about your hypothesis for the scientific community, you describe those as deficiencies in the hypothesis, because you do not have enough information to account for it; at least as far as when you're discussing it with scientists, correct?

A I put those forth as limitations that are not addressed by my hypothesis exclusively.

Q And when you discuss your hypothesis in the scientific community, you describe it as awaiting critical testing, correct?

A I don't usually use those words.

Q A starting point that can be critically tested -- doesn't that mean it's awaiting critical testing?

A No, it's being critically tested in different areas. In fact, the term await implies not yet happening. I mean, you're quibbling here. But if you want to quibble,

we can parse this out and deal with it.

But it's a hypothesis, and remains a hypothesis. It will remain a hypothesis, even after the medical, public, and legal opinion has probably weighed in on this or other hypothesis. It is going to remain that. This is the nature of science, and you know what I mean by this; that, in fact, science doesn't stop. If somebody pulls the plug on a certain concept or a certain disease, that it isn't declared finished.

So there's more to learn, and I'm open to that learning, and then I just put this forth as a hypothesis that is the best that can be summarized and formalized at this point in time.

Q As you explain to the scientific community when it is tested, it may be discarded, correct?

A Every hypothesis has the potential for that, yes.

MR. MATANOSKI: Thank you.

SPECIAL MASTER HASTINGS: Mr. Williams, anything further?

MR. WILLIAMS: No, thank you.

SPECIAL MASTER HASTINGS: Is there anything additional that the Petitioners want to put on today? I understand Dr. Deth is your only witness for today. That hasn't changed.

MR. WILLIAMS: Right, my understanding was, we

were going to devote the day to the Deth topics, and they were going to call somebody today to response if they wanted to.

SPECIAL MASTER HASTINGS: That was my understanding, as well.

MR. WILLIAMS: But we're finished with rebuttal with Dr. Deth.

SPECIAL MASTER HASTINGS: I just wanted to clarify that. Dr. Deth, thank you very much for being with us again. We appreciate it. You're excused.

THE WITNESS: Thank you.

(Witness excused.)

SPECIAL MASTER HASTINGS: What is the Respondent's plan?

MR. MATANOSKI: We are not going to call anyone today to respond to Dr. Deth, and we will not call on anyone tomorrow to respond Dr. Deth, with the one exception of the new paper, once the witnesses have looked at that, if they have any comment.

I would submit at that time that we move to have them testify about that, given that this was handed to us today. Had we been going forward with what we knew of what Dr. Deth was going to be relying on, then we would be perfectly comfortable with respect to witnesses.

I feel like we're probably going to be perfectly

comfortable where we are, after our witnesses take a look at that paper. But I do reserve to bring that up tomorrow with the witnesses that we have coming. But we may discuss that paper, and obviously we could address it at that time, if we do get onto it.

SPECIAL MASTER HASTINGS: So then if I'm understanding and I want to make sure, we've got no more witnesses for today, from either side. Tomorrow, we have Dr. Kinsbourne and Dr. Mumper for the Petitioners.

MR. POWERS: That's correct.

SPECIAL MASTER HASTINGS: All right.

MR. MATANOSKI: Just if I may, sir, so it's just Dr. Kinsbourne and Dr. Mumper, and not Dr. Greenland.

MR. POWERS: That's correct. Dr. Greenland will not be called in rebuttal.

MR. MATANOSKI: Thank you.

SPECIAL MASTER HASTINGS: Thank you; since we may have a longer day tomorrow, I have a couple of brief housekeeping matters I wanted to raise with you.

Just now as we're getting down to the end of this three week segment of the trial, and we have some more ahead of us; but I want to remind you both sides that a number trial exhibits have been submitted to us in paper form, discussed, and numbered. This is just a reminder that you'll need to file those formally in the King case, in the

Mead case, and in the third case to be named later, and both sides have them.

Right now, I have 11 for the Petitioner, 12 for the Respondent. I've got a list here, and I think if there's any confusion when it comes times to file them, about which is numbered, it's important that we get them filed at the same numbers that we used to identify them during the trial. Give Mr. Lowe a call if there's any question about that. But don't forget that we need to do that some time in the next few days after this trial is over.

The other issue I wanted to raise was the issue of the transcript correction process, which I think was a very good thing that we did after the theory one hearing in Cedillo last year, and in the other two cases, as well.

The timing of that process proved to be not ideal. As you may know, much of the briefing process was done before we had the transcript corrected. So we have briefs that have pagination that's not necessarily exactly the same.

So in terms of getting the pagination, it's also important to the court reporting service that we get that. It's much easier to change the pagination if we have that. So anyway, our idea is that we want the transcript correction process to take place as quickly as possible

here.

Now it's my understanding that nobody has ordered the transcript, special ordered it on the short notice or something. That's my understanding. So I guess we'll get the transcript something like 30 days from the end of the trial. Well, I don't know if we're going to get individual day-by-day segments earlier than 30 days.

But whenever we get them, what we did last time was the Respondents had someone, I think, listen to the whole tape and make suggested corrections. And then gave those to the Petitioners side. I hope we can do that process again, and I know we've got additional autism cases coming up, include the third case here. I hope that you will be able to spare somebody to start on that fairly soon after we get the transcript.

MR. MATANOSKI: I'll endeavor to do that, sir. I'm just a little reluctant to commit with my trial team behind me. They may start throwing things at me at this point. Maybe Monday it will be an easier pill to swallow, if I talk about it then.

SPECIAL MASTER HASTINGS: Okay, it's just the idea that we'd like to do that. So then when you both file your briefs, you just have to do it once with the proper page numbers, and it will be easier for everyone.

MR. MATANOSKI: And I know that we did actually

turn it around fairly quickly when we reviewed it last time.

SPECIAL MASTER HASTINGS: I think you did. So I'm just hoping we can. We can start that process as promptly as possible.

MR. POWERS: And I can say certainly, as was the case with Snyder, to the extent that we could stipulate, we could move this process along more expeditiously. Because I do agree, it's in everybody's interest to have the common set of paginations and references to the transcript in both sets of briefs, as that process goes forward. So we'll work to do that, too.

SPECIAL MASTER VOWELL: Filing the joint stipulation was the preferred way from the court reporting service.

SPECIAL MASTER HASTINGS: The other thing I wanted to raise today is just where you stand on the process of picking the third case.

MR. POWERS: I just told Respondent's counsel this morning, Special Masters, that we have medical records for three additional potential test cases. Those are being delivered on compact disk to Respondent within the next hour or two.

So they can do their limitations review, and review it for any issues indicating a concession might be appropriate, either on causation or an aggravation. That

will be forthcoming. I spoke with Lynn at the break.

Once those are exchanged and we get feedback from the Respondent on those issues, I think very quickly -- I mean, within days of hearing from them, we'll be able to specifically identify a case.

I do want to raise one issue that has complicate things; that the Asker case, which is still a viable potential test case, is one where there may be a conflict in that week of July, including other hearings in this proceeding; not in the omnibus, but in the vaccine program.

It's Kevin Conway and Sylvia Chin-Caplan and Ron Homer's firm's case; and trial counsel from that firm may have schedule conflicts with that week in July. So we obviously would endeavor to do everything that we could at our end, including working with the Special Masters and Respondent, if that is the test case, to see if those can be resolved to have that case heard in that week of July.

I know the Special Masters have indicated all along, including the Chief Special Master, of rescheduling other proceedings to accommodate test cases in the omnibus. We're aware of that and are actively looking to see what we can do. But that's the status. The Asker case is still very much a viable case, and records are going to DOJ for review. As soon as that is done, we will very quickly have a test case identified as the third case.

SPECIAL MASTER HASTINGS: What's the name again of the case where there is a possible conflict. Can you spell that for her?

THE REPORTER: I've got it.

SPECIAL MASTER HASTINGS: Okay, is there anything that we should talk about today before we break for the day?

(No response.)

SPECIAL MASTER HASTINGS: All right, then we are adjourned for the day, and we will commence for the last day of this three week extravaganza tomorrow morning at 9:00 a.m., thank you all.

MR. POWERS: Thank you.

(Whereupon, at 12:05 p.m., the hearing in the above-entitled matter was concluded.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 03-584V, 03-215V

CASE TITLE: In Re: Claims for Vaccine Injuries

HEARING DATE: May 29, 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 29, 2008

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