UNITED STATES
COURT OF FEDERAL CLAIMS

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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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IN THE UNITED STATES COURT OF FEDERAL CLAIMS

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INJURIES RESULTING IN)
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OR A SIMILAR)
NEURODEVELOPMENTAL)
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GEORGE AND VICTORIA MEAD,)
PARENTS OF WILLIAM P. MEAD,)
A MINOR,)
Petitioners,)
v.) Docket No.: 03-215V
SECRETARY OF HEALTH AND)
HUMAN SERVICES,)
)
Respondent.)

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

Thursday,
May 22, 2008

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

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

APPEARANCES:

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C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Respondent:					
Dean P. Jones	2692	2759	--	--	--
Thomas L. Kemper	2792	2862	2899	2904	--
	2847				
Patricia M. Rodier	2910	--	--	--	--

E X H I B I T S

PETITIONERS'

EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
Petitioners' Trial Exhibit 6	2763	--	Hansen Paper (2006)
Petitioners' Trial Exhibit 7	2778	--	Carvalho Paper (2008)

E X H I B I T S

RESPONDENT'S

EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
Respondent's Trial Exhibit 9	2691	--	Dean P. Jones Slide Presentation
Respondent's Trial Exhibit 10	2792	--	Thomas L. Kemper Slide Presentation

1 P R O C E E D I N G S

2 (9:00 a.m.)

3 SPECIAL MASTER VOWELL:

4 We're on the record in the omnibus autism

5 hearing in the Mead and King cases.

6 MR. MATANOSKI: Thank you. At this time the

7 government would Dr. Dean Jones, and Ms. Renzi will be

8 doing the examination.

9 SPECIAL MASTER VOWELL: All right.

10 What number are we up to?

11 SPECIAL MASTER HASTINGS: Number nine, I

12 think.

13 SPECIAL MASTER VOWELL: It looks like we

14 have another Respondent's exhibit, trial exhibit, and

15 we'll get that marked.

16 MS. RENZI: I believe we'll have two.

17 (The document referred to was

18 identified as Respondent's

19 Trial Exhibit 9.)

20 SPECIAL MASTER VOWELL: Dr. Jones, if you

21 would raise your right hand.

22 Whereupon,

23 DEAN P. JONES

24 having been duly sworn, was called as a

25 witness and was examined and testified as follows:

1 MS. RENZI: Good morning.

2 DIRECT EXAMINATION

3 BY MS. RENZI:

4 Q Dr. Jones, could you please state your name

5 for the record?

6 A Dean P. Jones.

7 Q Are you currently a professor of medicine at

8 Emory University?

9 A Yes.

10 Q Could you briefly describe your educational

11 background and training starting with your BS?

12 A As an undergraduate I was at the University

13 of Illinois with a major in Chemistry and a second

14 major in Biochemistry. I graduated in 1971. From

15 there I went to the University of Oregon, the Health

16 Sciences Center in Portland for a PhD in Medical

17 Biochemistry. I graduated from there in 1976.

18 Q After that?

19 A I went to Cornell University as a post-

20 doctoral fellow in Nutritional Biochemistry. From

21 there I went to the Karolinska Institute in Stockholm,

22 Sweden as a visiting scientist for almost two years.

23 Then came back to -- In that period of time I was in

24 Molecular Toxicology, that was my training area. I

25 went back to Oregon briefly before joining the faculty

1 at Emory University in 1979.
2 Q You moved to Emory in 1979?
3 A That's right.
4 Q You've been there ever since?
5 A Yes.
6 Q When did you move from the Department of
7 Biochemistry to the Department of Medicine?
8 A Approximately four and a half years ago. I
9 was in Biochemistry for 24 years. In the past several
10 years I've been in the Department of Medicine.
11 Q Could you please describe a few of your
12 recent honors and awards.
13 A One of my former honors was receiving the
14 Albert E. Levy Research Award from Emory University.
15 That's the most premier research award that the
16 university gives. They only give one award, and
17 that's given at graduation, so that's really quite a
18 distinguished honor from the university.
19 More recently I have, about ten years ago I
20 received a Nobel Fellowship to study in Stockholm
21 funded by the Nobel Committee. That was for research
22 in Molecular Toxicology.
23 Then more recently I have received the
24 Science and Humanity Award from the Oxygen Club of
25 California. That's an organization that is

1 principally Californian scientists, but it's really,
2 the president is now, it's an international group now.
3 Helmut Sies is the president. He's a German
4 scientist. It's really quite a distinguished honor.
5 Q Dr. Jones' curriculum vitae has been filed
6 as Respondent's Exhibit T.
7 Do you currently serve as a peer reviewer
8 for any journals?
9 A Yes. I regularly review manuscripts for
10 different journals ranging from Toxicology and
11 Nutrition to some of the premier international
12 journals such as Science and Nature, Nature Methods,
13 and so forth.
14 Q Have you ever served on an NIH study
15 section?
16 A Yes. I served for several years on two
17 different Toxicology study sections. I was the chair
18 of one of those study sections, Alcohol and Toxicology
19 I study section.
20 Q What were your duties?
21 A As the chair of the study section your
22 responsibility is to really oversee the peer review
23 process for the grants that you're reviewing, that
24 you're assigned to review. The most important aspects
25 are to maintain a fair and objective review, to really

1 follow the policies to make sure that the peer review
2 process is intact.
3 Q And could you please now describe some of
4 your current grants?
5 A One of my major grants is on oxidative
6 stress mechanisms, looking at nuclear, cell nuclei and
7 the oxidative stress protective mechanisms in cell
8 nuclei and then in the cytoplasmic compartments of the
9 cell. I am actually on several different grants, but
10 probably the major one is the, I'm one of the
11 assistant program directors on what's termed the
12 Clinical and Translational Sciences Award from NIH.
13 This is something in excess of a $22 million award
14 that is to support clinical and translational sciences
15 in, it's a consortium of Emory University, Morehouse
16 School of Medicine in Atlanta, and also Georgia
17 Institute of Technology.
18 Q Do you direct a lab at Emory?
19 A Yes, I actually direct two laboratories.
20 One is the clinical biomarkers laboratory. That is
21 the laboratory that is designed to provide oxidative
22 stress markers, cytokine measurements, inflammatory
23 markers, and really analytical services for
24 researchers throughout the university. Then I have my
25 own research laboratory that is focused on oxidative

1 reop biochemistry.
2 Q How many people do you supervise in your
3 labs?
4 A Currently there are four people in the
5 clinical biomarkers laboratory and I have four
6 students that I direct as well.
7 Q In addition to your lab you also have
8 teaching duties at Emory?
9 A Yes. I teach in the medical, in actually
10 two of the different medical courses. In nutritional
11 biochemistry mainly, and also in gastroenterology. I
12 teach in several of the pharmacology and toxicology
13 courses and also in the nutrition courses. Then as
14 needed throughout the university I give lectures on
15 metabolism and the new field of metabolonics.
16 Q You've published more than 325 peer reviewed
17 articles, reviews and book chapters, is that correct?
18 A Yes, that's correct.
19 Q And you've also published peer review
20 articles and of those peer reviewed articles many are
21 on your own research, is that correct?
22 A Yes.
23 Q How many of those peer reviewed articles are
24 in the field of sulfur metabolism?
25 A I haven't really counted them, but probably

1 about two-thirds of them.

2 Q Of those, how many focus on oxidative

3 stress?

4 A Most of them would have aspects of oxidative

5 stress. I would guess out of my total peer reviewed

6 papers I would have over 100 papers. A hundred

7 original research articles that would address

8 oxidative stress.

9 Q You have lectured both nationally and

10 internationally on the topic of oxidative stress, is

11 that correct?

12 A Yes.

13 Q Could you describe some of the lectures that

14 you've given?

15 A In general over the past 20 years or so I've

16 participated as an invited lecturer in five or more

17 national and international symposia. For instance,

18 during the last year, last fall I was an invited

19 speaker at a meeting in Jeju Island in Korea on redox

20 biochemistry. In January I was at a symposium that

21 was sponsored by the Japanese equivalent of our

22 National Institutes of Health, and also co-sponsored

23 by our National Institutes of Health, on biomarkers

24 of oxidative stress and health and disease. I've

25 recently been in Stockholm to give a lecture on

1 oxidative stress, a Society of Toxicology Meeting. I
2 gave two talks at that meeting in Seattle. In July
3 I'll be in Berlin at an international free radical
4 research meeting.
5 Q Dr. Jones, other than your testimony today
6 have you ever testified in a legal matter as an expert
7 witness?
8 A No, I have not.
9 Q You don't consider yourself to be an expert
10 in mercury toxicity, is that correct?
11 A That's correct.
12 Q You don't diagnose or treat children with
13 autism, is that correct?
14 A That's correct.
15 Q But you do consider yourself to be an expert
16 in the field of sulfur metabolism and oxidative
17 stress?
18 A Yes.
19 Q In addition to your expert report which wa
20 filed as Respondent's Exhibit S, you've also listened
21 to the testimony of Dr. Deth which was presented to
22 this Court on May 13th?
23 A Yes, I have.
24 Q And you've also reviewed the slides he
25 presented with his testimony?

1 A Yes, I have.

2 Q I'd like to point you to page three of Dr.
3 Deths' report where he states that, "Sulfur metabolism
4 is the single most important system to examine for a
5 contribution of Thimerosal in autism."

6 What I'd like you to do is explain to us as
7 simply as possible what sulfur metabolism is.

8 A Sulfur is the fifth most abundant element in
9 biological systems. Pretty much all of life depends
10 upon sulfur.

11 We have the proteins which constitute about
12 20 percent of our body. The proteins all contain two
13 sulfur-containing amino acids and these are the sulfur
14 amino acids methionine and cysteine. The function of
15 most of the proteins is actually dependent in one way
16 or another upon those sulfur amino acids. So sulfur,
17 it's ubiquitous in living systems and really is more
18 or less an essential component of all aspects of life.

19 Q We've also heard some testimony presented to
20 this Court that has discussed glutathione and its role
21 in sulfur metabolism and in the detoxification of
22 heavy metals. But glutathione does more than just
23 detoxify heavy metals, is that correct?

24 A Yes. Glutathione has a very important role
25 in metabolism. It is the major thiol in, major

1 sulfur-containing chemical. Now I didn't go through
2 the different forms of sulfur, and I can do that if
3 you'd like. The sulfur metabolism can get extremely
4 complicated.
5 What we're most interested in, I think, is
6 the thiol form, that's the reduced form of the sulfur.
7 That would constitute maybe one-third of the total
8 sulfur. The other forms probably are not so important
9 for the discussions here. So I'm going to talk about
10 the thiol form. The major thiol form is, as far as a
11 single chemical in the body is glutathione. It's the
12 most abundant thiol.
13 Q What is the role of glutathione in the body?
14 A Glutathione, this is actually a slide that I
15 put in. This is from some of our research that's
16 published which illustrates the point of the abundance
17 of glutathione.
18 This image that you see is actually taken
19 with the MRI, the common instrument that's in almost
20 all hospitals today for use for imaging of different
21 tissues. By changing the way the instrument is used
22 it's possible to identify and actually measure
23 different chemicals in the body. So this is actually
24 a scan done of human brain that illustrates signals
25 that are due to the different chemicals in the brain.

1 You can with this method measure about 20 to 30
2 different chemicals. The one that I have labeled here
3 glutathione, that is a signal from glutathione and it
4 actually shows you how abundant the glutathione is in
5 a living organism. We can actually see this non
6 invasively with this scanning technique in the human
7 brain.
8 Q That is Slide 2.
9 A Slide 2.
10 Q We'll move no to Slide 3 then.
11 A In Slide 3 I have listed the three major
12 detoxification functions of glutathione.
13 The one that has probably received the most
14 attention over the past 50 years is the function of
15 glutathione as an anti-carcinogen. The glutathione is
16 used to react with, as really the counter to reactive
17 chemicals that would otherwise cause mutations in the
18 DNA and would thereby cause mutations causing cancer.
19 So about a little over 50 years ago it was
20 recognized that many different chemicals that we are
21 exposed to, both the natural chemicals and manmade
22 chemicals, are activated in the body to reactive
23 chemicals, and that the most central way the body gets
24 rid of these is by reacting them with glutathione.
25 So probably, I think it would be safe to say

1 that glutathione is the most important anti-
2 carcinogenic chemical that we have in our body. So
3 that's one of the areas and that's been studied very
4 extensively over the past 50 years.
5 The second here is as an antioxidant. This
6 has also been known for about 50 years. It was
7 originally discovered in 1957 that the glutathione is
8 used for elimination of peroxides, in particular
9 hydrogen peroxide or H_2O_2.
10 If I get too fast, you just have to slow me
11 down.
12 The hydrogen peroxide is produced by the
13 body all the time. About one percent of all of the
14 oxygen that we breathe, and it turns out that this is
15 an enormous amount, if you think about it, it's about
16 a pound a day of oxygen that we consume. One percent
17 of that is converted to hydrogen peroxide so our
18 bodies have this oxidant load that is constant, that
19 we constantly have.
20 That one percent that is converted to
21 hydrogen peroxide, a large portion of that is
22 eliminated by glutathione through this antioxidant
23 activity of the glutathione. So this is really a very
24 important and central mechanism, function of
25 glutathione.

1 It does that more or less silently because
2 we have so much glutathione and the systems are so
3 efficient that it just handles it, but that is
4 ongoing.
5 The third here is the coenzymatic function
6 of glutathione. That is the glutathione is involved
7 in several other aspects of metabolism.
8 The only example I want to give is
9 formaldehyde. One of the main ways that we get rid of
10 formaldehyde is through a catalytic reaction, a
11 mechanism for getting rid of that involves using
12 glutathione as a coenzyme. In this reaction the
13 glutathione is not actually used up, it's just as a
14 catalyst. So as long as you have glutathione it will
15 bind to the formaldehyde and make the body more
16 efficient in getting rid of the formaldehyde.
17 I have some of these actually listed in the
18 next slide, Slide 4, which I don't put up for anything
19 to overwhelm you as far as this because it's far more
20 than, I mean there are experts in each aspect of this
21 slide. But what I wanted to illustrate by this was
22 that if you look at the first point on the anti-
23 carcinogenic aspects of the previous slide, on the
24 right-hand side of the slide, all of those glutathione
25 S transferases are functioning in that type of

1 chemistry.

2 So the right hand side then functions in

3 that detoxification of electrofiles or reactive

4 chemicals that we have. Those are functioning largely

5 in protection against cancer, although they protect us

6 in many other ways as well.

7 On the left hand side are the antioxidant

8 functions. These would be the ones in the center box,

9 the glutathione peroxidase. Those systems function as

10 antioxidants. You see there are many of those

11 antioxidant systems that are there. In the bottom

12 center is a box of the enzymes that are functioning in

13 metabolism.

14 So this isn't a comprehensive list, but I

15 pulled this off of one of the public databases of the

16 human genome, and these are enzymes that are encoded

17 by the human genome.

18 The main point of the slide is that

19 glutathione has many functions and that these in a

20 sense are competing functions, but the way the body

21 has, these mechanisms have evolved is to allow them to

22 work despite fluctuations in glutathione content.

23 Because as I will show later, there are natural

24 variations in glutathione content, and there are just

25 a very large number of reactions. In order for those

1 to work they have to be, the system has to be designed
2 so that activation of one doesn't inactivate the
3 other. So these are all going on simultaneously and
4 the glutathione, because of the very high abundance,
5 is able to support all of these different functions.
6 Q And glutathione is found in every cell in
7 the body?
8 A Yes, that's right. We synthesize
9 glutathione in every cell of the body. It's composed
10 of three amino acids. The amino acids are glutamate,
11 cysteine and glycine. And the capacity to synthesize
12 is really very high in cells. We can synthesize it.
13 But one of the interesting factors about glutathione
14 is that if you look at different organ systems, the
15 data, people usually get hyperbolic about the
16 importance of glutathione and want to say it's ten
17 millimolar. The reality is ten millimolar is what you
18 would see in a few tissues, liver and kidney for
19 instance. But many of the cells, for instance red
20 blood cells, may only have .2 millimolar. And in the
21 small intestine if you're in a fasting state it may
22 only be .1 millimolar. So there's really about a
23 hundred-fold, up to a hundred-fold concentration range
24 in different organ systems.
25 I think that's important in terms of

1 thinking about the way the systems work. We have so
2 much that even at that lowest level we have an ample
3 amount for carrying out all of this spectrum of
4 activities of the glutathione.
5 Q Dr. Deth's hypothesis is that Thimerosal-
6 containing vaccines disrupt sulfur metabolism and that
7 these disruptions cause autism. Is that your
8 understanding of Dr. Deth's hypothesis?
9 A Yes, that is.
10 Q But when you analyzed his hypothesis you
11 asked three questions, is that correct?
12 A Yes.
13 Q I'd like to bring up Slide 5 and have you
14 discuss it.
15 A As I was looking at Dr. Deth's report I
16 really felt that it needed to be broken into three
17 different questions because there are different
18 aspects of this, at least from my expertise on sulfur
19 metabolism and oxidated stress that really needed to
20 be considered. The first of these was the question of
21 whether the Thimerosal at the doses that are
22 administered, whether those would have a significant
23 effect on the sulfur metabolism.
24 Q Based on your knowledge and research in the
25 area of sulfur metabolism and glutathione, do you have

1 an opinion as to whether Thimerosal at the doses
2 administered in Thimerosal-containing vaccines can
3 significantly affect sulfur metabolism?
4 A I do have an opinion on that. I think that
5 what the data show is that the doses of Thimerosal
6 will not affect in a significant way the sulfur
7 metabolism.
8 Q Why is that?
9 A If we look at, I have on Slide 6 a
10 comparison of the total body thiol content and also in
11 reference, the sulfur amino acid intake compared to
12 what is in the literature as the cumulative load of
13 Thimerosal that would be expected from sort of a worst
14 case cumulative load of Thimerosal.
15 If you look at the top line here, total body
16 thiol, what I've tried to do here is express
17 everything in the same units. That's one of the big
18 difficulties in the literature is that there are many
19 different units that are being given. So I put these
20 into common units here. So there are some
21 approximations, I rounded things off. But I think it
22 will be clear from the way I've described this what
23 I've done.
24 So the total body thiol is really taken from
25 older literature where scientists took cadavers and

1 extracted the cadavers and measured in different organ
2 systems how much thiol is present. That number is
3 about 20,000 micromolar per kilogram, or about 20
4 millimolar. But I wanted to get it micromolar just to
5 have all common units here. So it's about 20,000.
6 If you look at the total body glutathione
7 one can estimate this in different ways also. I think
8 most people would say glutathione is approximately one
9 millimolar which would be a thousand micromole. My
10 estimate is that it's a little bit less than that, but
11 I think in a general sense it's in that range of 800
12 micromolar to 1000 micromole, so it's pretty much
13 consistent throughout a very large amount of
14 literature.
15 If we compare that then to what the
16 nutritional recommendations are for a zero to six
17 month old child, that would be equivalent to 500
18 micromoles per kilogram body weight.
19 What that's telling us is that on a daily
20 basis, the recommendations, we take in a lot of
21 sulfur. That sulfur is roughly equivalent to about
22 half the total amount that's in glutathione in the
23 body. But it's actually a much smaller fraction of
24 the total thiol in the body. So we really have a huge
25 total thiol content in the body. But the glutathione

1 is obviously an important component of that.
2 Q The thiols, the body thiols, also detoxify
3 and bind to heavy metals, is that correct?
4 A That's correct. Yes. So all of the thiols
5 would be potential binding sites for any heavy metal.
6 Q That's in addition then to the glutathione
7 which also does --
8 A Yes, that's right. So in addition to the
9 number of the glutathione that's in the cell, you have
10 a much larger amount of total thiol that would be
11 binding sites for the heavy metal.
12 That's the recommendation, the RDA would be
13 500. The question then is what do people actually
14 take in. Well, the RDA is set to more or less
15 guarantee that nobody has any deficiency, so that's
16 already set at a value higher than what almost anyone
17 would need. And so that's set at 500. So the
18 question then is how much do people actually take in?
19 I looked that up in the NHANES III, the
20 National Health Survey that's conducted by the Centers
21 for Disease Control. They give the values from their
22 evaluation, their analysis of where they actually
23 measure this in different individuals. Their range of
24 values I've taken here from the first percentile up to
25 the 99th percentile is in the range of 250 to 500

1 micromoles per kilogram body weight.
2 SPECIAL MASTER HASTINGS: I wanted to ask
3 about the RDA before you leave that topic. Is that,
4 RDA stands for recommended daily allowance?
5 THE WITNESS: Recommended dietary allowance.
6 Yes. And it's on a daily basis.
7 SPECIAL MASTER HASTINGS: Is that a maximum
8 or a minimum? I'm not following what that --
9 THE WITNESS: The way they set this is they
10 set that value to be one that they would expect
11 essentially nobody to have any extent of deficiency at
12 that point.
13 SPECIAL MASTER HASTINGS: In other words if
14 you get at least 500 you're not going to be deficient?
15 THE WITNESS: That's right. You're not
16 going to be deficient. So in that sense it's more
17 than you would need.
18 What the number of 250 to 500, that's the
19 NHANES. There might be some individuals in that range
20 in America who are getting at that lower end that may,
21 they may benefit from a little bit more, but there's
22 almost, I think you would conclude from this that
23 there's essentially no sulfur amino acid deficiency.
24 As long as the child is fed they're going to
25 be getting an adequate sulfur amino acid, judging from

1 that NHANES survey data. That's the way I would
2 interpret that data at least.
3 BY MS. RENZI:
4 Q Dr. Jones, what are the source of the sulfur
5 amino acids that we have in our diet?
6 A The main sources for people who eat animal
7 products would be obviously through eating, if the
8 child is consuming milk, it's going to be milk.
9 Animal products are very rich sources of sulfur amino
10 acids in general. It's really related to the animal
11 product intake.
12 Plant products in general have about half as
13 much to sometimes a bit less than half as much.
14 Particularly rich sources would be, for instance soy
15 milk. The legumes are among the best plant sources
16 for sulfur amino acids. Soy protein is one of the
17 proteins that's used in some of the milk, milk
18 substitutes, and that would be a rich source of sulfur
19 amino acids as well.
20 Q Back to Slide 6. How did you calculate the
21 Thimerosal --
22 A For a reference here I took the cumulative
23 dose of Thimerosal, I believe it was actually 180 was
24 in the article that I took that from. It's in my
25 report. I just rounded that up to make it easy for

1 comparison. Then asked the question, that's actually
2 a dose that was given, that's a total body dose,
3 independent of kilograms. I just assumed that was
4 given to a one kilogram child, so that would be a two
5 pound child. So this is really a very conservative
6 way to look at this. It's probably six-fold lower
7 than that if you had a six kilogram child, for
8 instance.
9 In any case, if you calculated that and
10 converted it to the same units, that would be
11 equivalent to one micromole per kilogram body weight.
12 So again, it's a very conservative way to look at
13 that. It may even be more reasonable to say .1 is
14 what the actual value would be. But I tried to be
15 conservative so there would be no question.
16 The comparison that you can see is that that
17 cumulative dose of Thimerosal, the estimation would be
18 that it's considerably less than what that daily
19 intake of sulfur amino acids would be, and certainly
20 very much lower than the body glutathione pool and two
21 thousand fold lower than the total body thiol.
22 Q You stated earlier that one of the roles of
23 glutathione is to react to chemicals in the body. Do
24 food items also contain the reactive materials that
25 our bodies use glutathione to deactivate? And we'll

1 turn to Slide 7.
2 A Yes, if we can look at Slide 7.
3 A few years ago we conducted a study to ask
4 the question whether there were glutathione reactive
5 materials in the foods that we eat. So we measured
6 this. This was also in peer-reviewed literature.
7 We measured the glutathione reactive
8 materials in foods. We looked at 142 different foods,
9 common foods that are in the American diet. I have
10 just listed two of them here but it gives I think a
11 good reference comparison.
12 That is if we look at the amount of reactive
13 materials just in an eight ounce glass of two percent
14 cow's milk, that number is, from the original paper,
15 was 21,700 nanomoles in that eight ounce serving.
16 If you convert that down to the same units
17 in terms of micromoles and assume that a child would
18 consume four ounces of milk in a serving, that would
19 be equivalent to 10 micromoles. That would mean one
20 four ounce serving of two percent milk would contain
21 ten times, more than ten times as much of the reactive
22 material.
23 If you look at other common foods that a
24 child might consume, for instance just bottled
25 unsweetened apple juice, the measured value in that

1 was 6600 nanomoles of glutathione reactive chemicals.
2 That would convert to four, if you took a four ounce
3 serving that would convert to four micromoles.
4 Again, that would be substantially above
5 that cumulative does of Thimerosal that would be
6 glutathione consuming or glutathione reactive
7 materials that would be in really a single serving.
8 Q So it takes more glutathione to react to a
9 four ounce glass of milk than it does to the
10 cumulative does in the Thimerosal-containing vaccines
11 that are normally administered over a six month
12 period?
13 A That's correct.
14 Q Dr. Jones, are there any natural variations
15 in glutathione levels?
16 A Yes. There are a number of different
17 variations. I have a slide here, also from published
18 peer reviewed literature, this is from my own lab, and
19 this illustrates in the yellow is the variation in
20 plasma cysteine over a 24 hour period.
21 So if you look on the X axis that is the
22 time of day, for this experiment what we did, these
23 are mean values for 62 individuals. We brought the
24 people into our clinical research unit, which is at
25 Emory University, and gave them all the same meals at

1 the same time of day, then took hourly blood samples
2 to measure what the concentrations were in the blood
3 as a function of time of day.
4 What you can see in the yellow, the cysteine
5 values, is that there is about a 30 percent variation
6 in the average cysteine over the time of day. Of
7 course this is an average, so some individuals had
8 somewhat more than this, some had somewhat less than
9 this.
10 In the blue and the green on the slide, is
11 the variation in glutathione as a function of time of
12 day. Notice that it's not in the same units as the
13 cysteine, and also notice that it's shifted in terms
14 of time with regard to when the maximum and minimum
15 values occur.
16 But the most important aspect of this is
17 that also with the glutathione there is about a 30
18 percent variation over the time, a 25 to 30 percent
19 average variation over the time of day that we see in
20 this average of 62 individuals.
21 Again, some individuals have somewhat more
22 variation than this, some have somewhat less variation
23 than this. But the point is this is all within normal
24 physiology that there is this type of variation.
25 Q We've heard about GSH/GSSG ratios which is

1 glutathione and oxidized glutathione ratios, is that
2 correct?
3 A Yes. If you look at, these are just the
4 cysteine and glutathione concentrations themselves,
5 but if you, at the same time we measured the disulfide
6 form. So in the way the systems work, we have a thiol
7 which is one-half, or just one molecule. When that is
8 oxidized it binds to a second molecule and that forms
9 a disulfide. So the reduced is the part that's
10 functional as far as what goes into proteins, as far
11 as in glutathione what's functioning in protection
12 against reactive chemicals, what's protecting against
13 oxidants. So it's the thiol form that's really the
14 most critical. A lot of the literature has used the
15 ratio or the redox potential, and I won't go into
16 that. That's far beyond what we need to talk about.
17 But that measurement of how good of a
18 reductant it is is really what that ratio is.
19 So these variations that you see in the
20 reduced form really reflect for the most part the
21 change in the redox state or the thiol disulfide
22 ratio, the reduced to the oxidized ratio throughout
23 the day.
24 So not only do you have a change in the
25 absolute concentration of the thiols, but you have a

1 corresponding variation in the oxidation reduction
2 state throughout the day. So that's a natural
3 variation.
4 There's actually another point that I think
5 is important on this slide, and that is --
6 SPECIAL MASTER CAMPBELL-SMITH: That's slide
7 number?
8 THE WITNESS: That's Slide 8, sorry.
9 So slide 8, there are several studies that
10 have not looked specifically at concentration of these
11 components but have rather looked at how fast the
12 system turns over.
13 So it's one thing to say okay, there's one
14 micromolar of glutathione, but it's another thing to
15 say how fast that one micromolar of glutathione turns
16 over. So how fast does it go into the blood, how fast
17 does it go out of the blood, how fast is it
18 incorporated into the cells, and in that cycling, that
19 dynamic cycling of metabolism.
20 So those measurements are really very
21 interesting and I think very pertinent to this
22 discussion because what those numbers, what they
23 measure out to show is that the turnover of the system
24 is approximately one micromole per kilogram body
25 weight per minute.

1 In other words that same number that we
2 talked about as far as that sort of upper limit of the
3 total Thimerosal load from multiple dosing, that's
4 equivalent more or less to the amount, the rate of
5 turnover on a per minute basis.
6 So within one minute there is more thiol
7 being turned over in terms of normal metabolism than
8 the total load of the Thimerosal from that cumulative
9 dose.
10 BY MS. RENZI:
11 Q And I think before we go, I think that's
12 illustrated on our next slide. But before we do that,
13 if you were to receive a Thimerosal-containing vaccine
14 would that change at all this chart that we see on
15 Slide 8 of the natural variations?
16 A I wouldn't expect for there to be any effect
17 at all. The amount of Thimerosal, it simply wouldn't
18 be delivered within one minute, so the total turnover
19 is so fast that it would have, I don't think it would
20 have any detectable effect. I don't think any
21 instrumentation is good enough to, if it had an
22 effect, to even be able to detect it.
23 Q If we can go to the next slide --
24 SPECIAL MASTER CAMPBELL-SMITH: That would
25 be slide number nine?

1 MS. RENZI: Number nine. Thank you.
2 BY MS. RENZI:
3 Q We're going to go back and look at --
4 A This was the basis for going to Slide 9.
5 Q Just move to Slide 9.
6 What you were saying, Dr. Jones, that it
7 would take less than a minute for the body to replace
8 the amount of glutathione that is used to bind and
9 deactivate a Thimerosal-containing vaccine, even if
10 the entire six month load were administered at one
11 time?
12 A Yes.
13 Q Now Dr. Deth relies on several in vitro
14 studies to support his causal hypothesis involving
15 sulfur metabolism. Do you consider in vitro studies
16 to be a reliable way to determine in vivo toxicity?
17 A No, I do not.
18 Q I want to draw your attention to page four
19 of Dr. Deth's report where he discusses in vitro
20 studies in his laboratory, and the data has not been
21 published. He states that, "The threshold effect for
22 Thimerosal reduction of GS8 is approximately .1
23 nanomolar indicating a remarkably potent influence on
24 cellular redox status in human neuronal cells."
25 Can you read that?

1 A Yes.
2 Q Have you reviewed the published in vitro
3 data which measured the concentration dependence of
4 Thimerosal depletion in glutathione?
5 A Yes, I did. When I read Dr. Deth's report
6 this particularly caught my attention because that .1
7 nanomolar of glutathione is, that effect on
8 glutathione is simply at such a remarkably low level
9 that there's no analytical technique that I know of
10 that would be sensitive enough to pick up that type of
11 an effect on a glutathione system. So that prompted
12 me to go back and review the literature on the dose
13 dependence, the in vitro studies, of the dose
14 dependence of toxicity of the Thimerosal in the in
15 vitro studies, which I included in my report for
16 comparison of the published peer reviewed, published
17 literature on the concentration dependence of the
18 Thimerosal toxicity.
19 SPECIAL MASTER VOWELL: Doctor, can we break
20 that into two pieces? Are you saying that there was
21 no way to detect that effect?
22 THE WITNESS: What caught my attention was
23 the fact that if you put a chemical in that you're
24 claiming to have an affect on the glutathione, then
25 you have to be able to measure the change in

1 glutathione at that level. I have developed methods
2 for glutathione, in fact I have one of the major
3 methods that's in use for glutathione, and the level
4 of, the sensitivity of the method, it's the best
5 method available as far as I know, and the sensitivity
6 of that method isn't good enough to be able to detect
7 a .1 nanomolar change. So that's what caught my
8 attention to this. Just that number did not seem
9 credible.
10 That's not passing any judgment because I
11 don't know what method he used for his measurements
12 because that wasn't in the report of how they measured
13 glutathione.
14 SPECIAL MASTER VOWELL: But you're saying
15 you know of no method.
16 THE WITNESS: I know of no method. That's
17 what I'm saying. So that prompted me to go to the
18 literature to look at what other people had reported
19 as far as the concentration of Thimerosal that would
20 cause toxicity in the in vitro study.
21 Is that clear?
22 SPECIAL MASTER VOWELL: That's clear. I
23 just wanted to make sure.
24 BY MS. RENZI:
25 Q And you've listed that literature on page 11

1 and 12 of your report.
2 A Yes. And I was not exhaustive on this.
3 What I tried to do, I was not selective either. These
4 were just ones that I went to. These were the first
5 ones that I ran across in this literature. They
6 seemed to be relevant to me and actually seemed to be
7 extremely consistent with what they showed. If you
8 look at the Park et al, they found that 2.9 micromolar
9 killed 50 percent of these inner medullary collecting
10 ducts. Those are kidney cells. 9.5 micromolar killed
11 50 percent of embryonic kidney cells. Then gastric
12 cancer cells, it was between five and 10 micromolars.
13 In the Herman paper, neuroblastoma model,
14 very similar concentration. 2.5 micomolar kills the
15 cells but not one micromolar.
16 In this SKNSH neuroblastoma cell line of
17 Humphrey, they also found 2.5 to 5 micromolar causing
18 cell death.
19 There was one paper that showed a little bit
20 lower value with a nanomolar range, but this was an
21 unusual one because these cells, as far as I know,
22 require a specific growth factor in order for the cell
23 to survive.
24 So they took that growth factor out, which
25 is going to cause the cell to die anyway, and then

1 they put in mercury, they put in the Thimerosal and
2 found an enhancement of the toxicity of these already
3 dying cells.
4 So I think that is actually stretching the
5 point as far as sensitivity. I would read those data,
6 the cumulative data that I see in the published
7 literature is really consistent with the toxicity and
8 the range of in the low micromolar range of the
9 Thimerosal.
10 SPECIAL MASTER HASTINGS: Let me ask a
11 question at this point. I had a question when I first
12 read pages 11 and 12 of your report, and as I reviewed
13 it last night.
14 You see at the bottom of 11 you indent a
15 paragraph. It goes on to page 12, those two
16 paragraphs. It wasn't clear whether you were quoting
17 from something earlier. Why --
18 THE WITNESS: No. I --
19 SPECIAL MASTER HASTINGS: That's just part
20 of your report, where you actually talk about the in
21 vitro evidence.
22 THE WITNESS: That was because, I indented
23 that just because in this case I explicitly went to
24 the literature and reviewed those points, as opposed
25 to, most of the other work I was largely relying upon

1 my own expertise that I am completely knowledgeable
2 on. I'm not an expert in mercury toxicity. I am not
3 an expert in Thimerosal toxicity. I want that to be
4 completely clear. I went to this as an objective
5 scientist asking the question why is this value of
6 nanomolar that Dr. Deth cited, why is that
7 inconsistent with the way I would think about
8 toxicity.
9 So when I went to the literature I found
10 that the bulk of the literature that I saw did not
11 give toxicity in the nanomolar region. It gave the
12 toxicity in the micromolar region.
13 SPECIAL MASTER HASTINGS: But these two
14 paragraphs are your own summary of your literature
15 review.
16 THE WITNESS: That's right.
17 SPECIAL MASTER HASTINGS: Thank you.
18 THE WITNESS: I don't want to imply that I
19 was exhaustive, because I am not an expert in that
20 field. These are the papers that I picked up, and as
21 I went through them they were consistent with each
22 other.
23 BY MS. RENZI:
24 Q Doctor, how can culture conditions determine
25 what concentration you need to cause toxicity? We're

1 on Slide 9.
2 A We have done a lot of in vitro toxicity
3 research. I have put an example of the type of
4 problem that you can have in trying to do
5 extrapolations from in vitro work to in vivo work.
6 One of these is illustrated here in Slide 9.
7 What this shows is that in tissue culture in
8 general you have cells growing on a single mono-layer
9 on a dish. So at the bottom of the dish there's a
10 very very small volume of cells. Above that you have
11 your culture medium which contains the nutrients for
12 those cells to grow. This is really to illustrate the
13 point, different investigators will do this
14 differently. They'll use different size of dish, they
15 will use different numbers of cells, they will use
16 different volumes. So those are oftentimes not
17 specified at all. Sometimes it's relevant in
18 experimental design, sometimes it's not.
19 If you have a chemical, however, that is
20 accumulated in the cells then that volume of the
21 culture medium above the cell relative to the volume
22 of the cells become highly relevant. Now the cells
23 are accumulating the toxic chemical that you add.
24 So the example that I've shown here is if
25 you had one milliliter of culture medium, in other

1 words a thousand microliters on the left hand side,
2 that would partition into approximately 999
3 micrometers of culture medium relative to the cell
4 volume which would typically be one microliter volume,
5 sometimes even less than that.
6 What that means is if you put in a chemical
7 on the right hand side at one micromolar, so you add
8 it at one micromolar, if it accumulates in the cell,
9 in this hypothetical example here, 100 percent of it
10 accumulated, you would accumulate that to 1000
11 micromolar in the cell.
12 So this now becomes a function of the
13 relative amount of the volume that you have relative
14 to the number of cells, as to how much of the toxic
15 load you're actually going to put onto the cells.
16 Is that point clear?
17 SPECIAL MASTER VOWELL: Let me just restate
18 it to make sure I understand it.
19 If I have something that is in volume,
20 you're using 1000 micromolars? Only one of that is
21 cells.
22 THE WITNESS: Yes.
23 SPECIAL MASTER VOWELL: Those cells uptake a
24 particular toxic substance.
25 THE WITNESS: Yes.

1 SPECIAL MASTER VOWELL: At 100 percent of
2 that toxic substance.
3 THE WITNESS: Yes.
4 SPECIAL MASTER VOWELL: Rather than using
5 ratios that say it's one micromolar to a thousand, it
6 would really be, the cells would have that entire
7 amount.
8 THE WITNESS: Yes. That will happen for
9 chemicals that react with thiols. They will
10 accumulate into the cells and oftentimes it will be
11 nearly 100 percent will accumulate.
12 What that means then is if you put, for
13 instance in this case if you put a half a mil in there
14 of one micromolar, the dose at the cell would only be
15 half as great as if you put in a full milliliter.
16 So in effect simply by changing the volume
17 that you're putting above the cells with the same
18 concentration, you can deliver a different amount of
19 toxicant to the cells. This is really a problem for
20 comparing literature because oftentimes it's simply
21 not stated how many microliters of volume that's
22 added.
23 The other side of this is actually I think
24 in the next slide, Slide 10. You can see the
25 importance of this comparison in terms of the thiol

1 content. In that one microliter of cell volume if one
2 measured how much the total thiol content would be,
3 commonly it's in that range of one thousand to ten
4 thousand micromolar in those cells.
5 That means that if indeed you've put in one
6 micromolar of a chemical with this type of a volume to
7 a cell ratio, you're going to now be consuming a large
8 fraction of the total thiol in the cells.
9 Indeed what you see, if you go through the
10 literature, and just a broad spectrum. If you look at
11 different in vitro toxicity studies, what you will
12 find is that a very very very large number of
13 chemicals that react with thiols will cause toxicity
14 in this range, in this low micromolar range.
15 So in a way that's a very non-specific
16 effect because you're putting in so much of your
17 material that you're going to be really overwhelming
18 the thiol systems. You're putting in almost as much
19 of the reactive material, in some cases if you went up
20 to ten micromolar you probably would be putting in
21 enough to react with essentially every thiol in the
22 cell. So it's grossly out of line with what you would
23 see in vivo.
24 In vivo you have less extracellular volume
25 than you have cellular volume.

1 We can stop on that if you need to think
2 about that one. These are different concepts.
3 BY MS. RENZI:
4 Q Also the fewer the cells in the culture
5 medium the lower the toxicity threshold will be
6 because the more the administered substance goes to
7 each cell, is that --
8 A Yes. I think in Slide 11 I have this point
9 made.
10 The more typical does response curve that
11 you would see for these experiments is that you would
12 have essentially no toxicity at lower concentrations.
13 Once you achieve a range where you have toxicity, most
14 of the cells die at the same time. What that says is
15 that all of the cells have the same mechanisms within
16 them. You don't have some cells that are going to
17 respond at a very very low concentration and other
18 cells that are responding at a very high
19 concentration. Rather, they're all responding
20 similarly. That means you really have a good cell
21 culture.
22 What you can see from that example is that
23 if you did your experiments, if you tried to select
24 conditions you could use, instead of using a million
25 cells in your dish you could use 100,000 cells in your

1 dish. So if you did that, now you only need one-tenth
2 as much of your toxic species in order to get the
3 toxicity.
4 So in effect this curve would be shifted to
5 the left in order of magnitude.
6 SPECIAL MASTER VOWELL: And you're referring
7 to Slide 11?
8 THE WITNESS: Slide 11, yes. It would shift
9 that curve to the left.
10 The difficulty, so I cannot pass judgment on
11 these papers in terms of this issue because none of
12 them that I could tell really gave enough explicit
13 information as far as the volume that was used, as far
14 as the number of cells that was used, to really allow
15 those type of comparisons. That is also the
16 difficulty that I had with Dr. Deth's statement,
17 because without that type of information it really
18 isn't possible to know whether or not conditions were
19 selected to enhance the toxicity.
20 There are, of course, other ways that one
21 can change the culture conditions.
22 SPECIAL MASTER CAMPBELL-SMITH: Let me just
23 ask this question so I can be clear. With the
24 difficulty that you have expressed for in vitro is,
25 particularly in perfect conditions when you have a

1 uniform cell culture, a good cell culture that reacts
2 the same.
3 First of all it's a mono type of cell.
4 THE WITNESS: That's right.
5 SPECIAL MASTER CAMPBELL-SMITH: And there's
6 no extracellular material to absorb the added
7 toxicant. So the cell bears the full burden of the
8 toxicant.
9 THE WITNESS: That's right.
10 SPECIAL MASTER CAMPBELL-SMITH: And unlike
11 the natural in vivo circumstance where you have
12 extracellular area and you also have different types
13 of cells that would modulate the effects.
14 THE WITNESS: Absolutely.
15 SPECIAL MASTER CAMPBELL-SMITH: Those are
16 the reasons why it is difficult to do the translation
17 from in vitro to in vovo.
18 THE WITNESS: Yes, exactly. That's the
19 difficulty of being able to compare Dr. Deth's data
20 also to the other in vitro data. Because if you take
21 into account the fact that you can do your cell
22 culture with or without albumin, for instance.
23 Albumin is a component of blood and it binds a lot of
24 chemicals. Albumin has, in human plasma, there's 200
25 to 400 times as much thiol in the albumin in the blood

1 as there is glutathione in the blood.
2 So if you, in cell culture, most people
3 would have albumin present. If you put albumin
4 present then it's going to change how much of your
5 Thimerosal will get into the cells. At least in
6 general that's the way I would -- I don't know that to
7 be a fact on Thimerosal because I haven't done those
8 studies, but in general if you had a serum in the
9 culture medium it will change the sensitivity of the
10 cell to the toxicant, so it will shift that curve.
11 So if you omit albumin from your culture
12 medium you can shift that curve over.
13 If you change your ratio of the volume to
14 the cells, you can shift that ratio over.
15 If you omit growth factors like the nerve
16 growth factor that's essential for the cell to
17 survive, for many of these neuronal cells to survive.
18 If you omit that, you can shift the curve over.
19 So really without knowing, and that's one of
20 the values of peer review, because once the data goes
21 into peer review, the reviewers usually will be
22 careful as far as identifying a lot of these problems.
23 Sometimes they won't. Sometimes things will go
24 through without that critical review. But
25 nonetheless, the peer review does provide some

1 assurance that those conditions have been adequately
2 described so you can understand what was done.
3 Especially in something like this, if
4 someone were to try to publish something that is three
5 or four orders of magnitude, a thousand fold or ten
6 thousand fold out of line with half a dozen papers
7 that have already been published, questions would be
8 raised. What are the differences? Why are all these
9 other papers wrong and why are you right? Those
10 questions would be raised.
11 That's my comment on that, and I don't know
12 if there's anything else you want --
13 SPECIAL MASTER HASTINGS: Just before you
14 answered Special Master Campbell-Smith's question in
15 your discussion of Slide 11 you said that's why I have
16 trouble with, you said "these papers" or "those
17 papers" in the plural.
18 I wasn't clear what papers you were
19 referring to at that point.
20 THE WITNESS: I'm not sure. I guess what I
21 was saying is the, I am uncomfortable with the
22 discrepancy of Dr. Deth's report.
23 SPECIAL MASTER HASTINGS: So you were
24 referring strictly to Dr. Deths' paper --
25 THE WITNESS: Dr. Deth's report relative to

1 the others. I think as a scientist what we're trained
2 to do and what we've learned to do is you have to
3 trust the scientific literature. That's really, you
4 have to trust the published literature was done as
5 honestly and with as much integrity as possible. When
6 the same observation or similar types of observations
7 are obtained in several laboratories you would tend to
8 give that more credibility than an unpublished report
9 where you didn't have the understanding of why the
10 systems were different and why the bulk of the
11 published literature was wrong. I think that would be
12 the way I would try to say it.
13 I may have misspoken, I'm not really sure.
14 BY MS. RENZI:
15 Q So just to clarify this although probably no
16 clarification is needed, but the stark differences
17 between the published peer reviewed literature and Dr.
18 Deth's data, in your experience as a researcher, can
19 you draw conclusions on the reliability of Dr. Deth's
20 data?
21 A Again, without actually knowing the
22 conditions in which he did it and without really
23 understanding those details, the face value, I have to
24 conclude that I would question. I would not put
25 credibility in Dr. Deth's statement that it's

1 sensitive of the nanomolar concentration. That seems
2 to be inconsistent with the bulk of the data that I've
3 looked at.
4 Q One of the studies relied upon by Dr. Deth
5 is a 2005 Jill James study which is Petitioner's
6 Master List 7. Did you review this paper?
7 A Yes, I did.
8 SPECIAL MASTER VOWELL: You're on Slide 12?
9 THE WITNESS: Slide 12.
10 BY MS. RENZI:
11 Q Did you reach any conclusion about its
12 relevance to what occurs in vivo with Thimerosal-
13 containing vaccines?
14 A I really concluded that these conditions
15 were probably irrelevant to the question of in vivo
16 toxicity because the concentrations were really out of
17 line. I went through the calculations here on this
18 slide and it's also in my written report. with the
19 James paper they used ten micromole per liter
20 Thimerosal and I just used this value of 200
21 micrograms per micromole, that's the mercury content.
22 But that's equal to 2000 micrograms per liter there on
23 the right hand side, just the ten times the 200.
24 So the 2000 micrograms per liter would be
25 two micrograms per milliliter.

1 If you assumed that in the one milliliter
2 culture that you had one miligram of cells at that
3 bottom, then what that would mean, that accumulated in
4 the cells there in the middle, you can see two
5 micrograms. That would be equivalent to two
6 micrograms per milligram of cells. Of course the two
7 micrograms per milligram of cells would be equivalent
8 to two milligrams per grams of cells if there were
9 avid uptake of the cells in the white there. There
10 would be two grams per kilogram tissue.
11 So if you go back to Ball et all estimate
12 for the total body load from the multiple Thimerosal-
13 containing vaccines of 200 micrograms, that's equal to
14 0.0002 grams.
15 So what that would say is that in the same
16 units, if that were in a one kilogram child, you would
17 have, a rough estimate, 10,000. I have listed here as
18 greater than 1,000 but it would really be closer to
19 10,000-fold higher concentration of the Thimerosal in
20 these in vitro experiments than would be relevant to
21 the actual dosing in vivo.
22 Q This slide just illustrates the problem of
23 trying to extrapolate in vitro studies into in vivo
24 conditions.
25 A That's correct. And that's really the

1 difficulty is the total Thimerosal load is simply so
2 low relative to what the cells see in these in vitro
3 conditions.
4 Q Dr. Jones, I'd like to take a look at the
5 next slide, Slide 13, which was presented by Dr. Deth
6 as his Slide 24.
7 We've heard Dr. Aposhian testify that liver
8 contained approximately 10 millimoles of glutathione
9 and that is where glutathione is most concentrated.
10 What does this graph represent?
11 A If you look at this, the concentration here
12 that's given, or the content, starts off at about 750
13 nanomoles per milligram protein. So in general
14 tissues, mammalian tissues, whether it's brain or
15 liver, will contain about 20 percent protein and a
16 little over 70 percent water. So what one can say is
17 that for one milligram of protein there would be
18 approximately 3.5 microliters of water.
19 So you can actually convert these numbers in
20 a rough way to millimolar, in a very direct way really
21 to what the approximate millimolar concentrations
22 would be in these experiments.
23 If you do that, those numbers, it would be
24 approximately 3.7 microliters of volume that would be
25 750 nanomoles would be in 3.7 or so microliters. That

1 calculates out to about 20 millimolar glutathione.
2 So there's clearly something wrong with the
3 analytical methodologies here. Again, I don't know
4 what methodologies were used, I don't know how it was
5 referenced, but it really puts into question all of
6 these data because the data are just inconsistent.
7 There's really no tissue in the body that has 20
8 millimolars glutathione. That's far in excess of what
9 tissues would have.
10 Q Dr. Jones, is it your opinion that
11 Thimerosal-containing vaccines play no significant
12 role in sulfur metabolism?
13 A Yes. I think at the doses that are included
14 in the Thimerosal-containing vaccines, that that does
15 from, my understanding of what that dose is, that
16 would be at a level which would simply be too low to
17 have any significant effect on the glutathione system.
18 Q Your second question is, at doses where
19 effects on sulfur metabolism occur, are these adverse
20 effects. I'd like you to address that.
21 A This question is, again going back to Dr.
22 Deth's written report, I felt it was important to
23 break his overall consideration into three different
24 questions because the first aspect is whether or not
25 you're going to expect a change in sulfur amino acid

1 from that level of Thimerosal. But the second one
2 then is, if you had a detectable effect, that is even
3 if it were high enough that you did have a detectable
4 effect, would you expect that to be an adverse effect.
5 For this I have in here, unfortunately, a
6 very complicated slide so I think in the next one,
7 Slide 15. But hopefully I have simplified it enough
8 so it's not unreasonable as far as the major point.
9 So this illustrates one of the central
10 systems that the body has to protect against agents
11 which would perturb the glutathione system.
12 The way this system works is that if you
13 have a low level of any sort of component that's going
14 to perturb the glutathione system, there is this Nrf-2
15 system, and it's not important that you know what Nrf-
16 2 stands for. This Nrf-2 system is bound to a sensor,
17 and this sensor measures things that react with
18 thiols. It actually has 26 different cysteines,
19 different thiols in this one protein called Keap-1.
20 So the way the system works is if you have
21 something, these are very very sensitive thiols. If
22 you have something that perturbs the system, this
23 Keap-1 is more or less a sensor for that. What it
24 does is it releases the Nrf-2, and the Nrf-2 then
25 which is normally kept in the cytoplasm away from the

1 genetic material, this moves into the nucleus and
2 interacts with the genetic material and turns on
3 protective systems.
4 SPECIAL MASTER HASTINGS: In your last
5 couple of sentences you used the word "sensor". It's
6 S-E-N-S-O-R?
7 THE WITNESS: Yes. To detect something, the
8 usual English word.
9 Really, I just use that sort of as an easy
10 way to describe it. What it is is a protein that has
11 26 different cysteines sitting out in its structure.
12 And when these chemicals come in, whether it's an
13 oxidant or an electrofile, a reactive chemical, or
14 even some metals will interact with this. What it
15 does is it changes the structure and causes this
16 protein, the Keap-1 to let go of this other protein
17 that it normally binds to. That other protein that it
18 normally binds to is called Nrf-2. That now moves
19 into the nucleus. Once it goes into the nucleus it
20 can interact with the DNA in the nucleus.
21 In that process it turns on increasing the
22 proteins that are needed, these other systems, these
23 antioxidant systems, these other systems that are
24 protective against agents that will perturb the
25 glutathione system.

1 So normally what happens is, and this
2 happens to us every day when we eat. If we go out and
3 run this happens. There are many different things
4 that will cause this. It increases the system and it
5 increases our protective mechanism.
6 I think the main point of this is that we're
7 constantly exposed to these agents. It's a normal
8 protective mechanism. So if one sees a change in the
9 glutathione system, one can't just assume that it's a
10 bad change. It can in fact be a protective change
11 because that is the way the system response.
12 I think in Dr. Johnson's testimony, Dr.
13 Johnson is an authority in that mechanism. I think he
14 talked about that system of where you initially see a
15 decline and then in the time course it comes up and
16 that is part of the normal signaling mechanism that
17 controls the system.
18 BY MS. RENZI:
19 Q It's a compensatory response to --
20 A Yes. It's a protective response, really.
21 Q What sorts of things induce this
22 compensatory response in the glutathione system?
23 A I have listed some of these. There are
24 many of these that are common in the diet. This is
25 the reason that your mother or grandmother told you to

1 eat your broccoli and cauliflower and brussels sprouts
2 and so forth. Chemicals that do this are found
3 commonly in these cruciferous vegetables. They're
4 also common in other foods such as garlic and onion.
5 They're present in things such as green tea that are,
6 there are many -- these are widespread chemicals in
7 the diet that will activate this. You can activate it
8 with a number of other mechanisms that will cause
9 changes in the system.
10 Q So like I never ate my vegetables as a
11 child. Does this mean I wouldn't have had any of
12 these compensatory responses?
13 A No, you still have the compensatory
14 responses. How much they are activated, it will vary
15 really on an individual basis, on a day to day basis.
16 We all have these protective mechanisms. The most
17 important thing is that simply by measuring the level
18 itself, measuring the level of glutathione itself and
19 the change in the level of glutathione itself, you
20 can't assume whether it's a good thing or a bad thing
21 to see a change because the way the system responds
22 is that an initial small decline can cause a
23 tremendous subsequent increase in the response.
24 For instance, there's a chemical in apples
25 called dimethyl fumarate. The dimethyl fumarate, if

1 you drink apple juice, it will activate the system.
2 So initially you'll see a small decline in the
3 glutathione levels, but then the glutathione levels
4 will rise at subsequent times.
5 SPECIAL MASTER VOWELL: And this is the
6 point that was being made two days ago about not
7 carrying the experiment out over a long enough time
8 period.
9 THE WITNESS: That's right. Yes.
10 BY MS. RENZI:
11 Q In summary, what does this data show you?
12 we'll go to slide 17.
13 A I think in terms of the second question
14 then, at doses where you do see effects on sulfur
15 metabolism, can you just assume that those are adverse
16 effects? I think that the normal diurnal variation
17 seen is greater than that which would occur due to the
18 Thimerosal dosing.
19 So in that sense one wouldn't say that the
20 variation would be an adverse effect. That's just a
21 normal physiologic variation.
22 Then with regard to the Nrf-2 system,
23 there's really a broad range of agents which activate
24 that system to cause protective responses so that one
25 cannot conclude that simply modification of

1 glutathione implicates toxicity. That is an
2 unreasonable, an incorrect conclusion to make.
3 So I think the bottom point there is that
4 modification of glutathione per se cannot be taken as
5 evidence of adverse effects.
6 Q You've demonstrated that Thimerosal-
7 containing vaccines do not have a significant effect
8 on sulfur metabolism, and even if they had effects, we
9 couldn't assume that the effects were adverse.
10 But putting that aside, your answers to the
11 first two questions you presented, and we're on Slide
12 18, if there were adverse effects on sulfur
13 metabolism, could you assume that they'd be a cause of
14 autism?
15 A For this what I did was I went through, to
16 try to address this I went through Dr. Deth's, I
17 listened to Dr. Deth's presentation of his hypothesis.
18 What I'd like to do is go through briefly what I
19 consider to be critical points in this hypothesis and
20 what I felt were questions. I think we can go to this
21 overhead.
22 MS. RENZI: That would be fine.
23 Special Masters, what I think we'll do here
24 is, he's going to probably write on some slides. You
25 have in front of you the reference, and then we will

1 submit this as Trial Exhibit 10 with his writings and
2 we'll get you copies during the break.
3 BY MS. RENZI:
4 Q You found critical flaws with the mechanisms
5 hypothesized by Dr. Deth, is that correct?
6 A Yes. So what I've done here is in this,
7 I've just taken Dr. Deth's Slide 18 where he has
8 outlined his mechanism in terms of the sulfur, the
9 alterations in the sulfur metabolism. What I want to
10 start with is number one here where he has described a
11 pathway for glutathione being converted through
12 cysteinylglycine to cysteine as the supply mechanism
13 for delivering cysteine to the neurons.
14 In his evidence that he presented for the
15 mechanism, he relied for support for this particular
16 aspect of the mechanism upon the data from an article
17 of Jill James and coworkers --
18 SPECIAL MASTER VOWELL: This is Slide 20?
19 THE WITNESS: This is now Slide 20 that you
20 have.
21 This is Dr. Deth's Slide 13.
22 What I'd like to point out is that the
23 chemical, these are all plasma values. I believe
24 you've already heard testimony that it's really
25 unreasonable to use plasma values as indicators of

1 what's happening in the brain, so there's already a
2 question with regard to the validity of using these
3 data to support the hypothesis because there's really
4 abundant literature that the blood levels do not
5 directly reflect the brain concentrations.
6 But nonetheless he used this in support of
7 his argument.
8 Specifically he pointed out here the 36
9 percent decline in the free glutathione as being a
10 very important component.
11 So we'll go back to the overall scheme in
12 just a moment, but what I would like to point out is
13 what's herein the green box is cysteinylglycine. Now
14 the cysteinylglycine concentration, if you notice, is
15 the highest concentration of all of the components in
16 this list. So this is the one that's in most
17 abundance in the plasma according to these
18 measurements.
19 Generally the higher the abundance the
20 greater the analytical accuracy. So one would have to
21 assume that these would probably be the best numbers
22 in the whole list because they're the ones that are
23 the most abundant, they're the easiest to see, easiest
24 to measure.
25 What's very important here is that there's

1 no significant difference between the control and the
2 autistic in terms of the concentration of the
3 cysteinylglycine.
4 So if we go back to that scheme of the
5 pathway what you'll notice from the pathway is that --
6 SPECIAL MASTER VOWELL: We're back on Slide
7 19.
8 THE WITNESS: That's back to Slide 19. That
9 is a critical intermediate in the pathway. In other
10 words, what he is arguing is that you have a decline
11 in the glutathione which is relevant to the downstream
12 effects, but ignoring the fact that the critical
13 obligatory intermediate, that is the cysteinylglycine,
14 doesn't change. So that's completely inconsistent
15 with that hypothesis.
16 So even if you believed his arguments that
17 the plasma values are relevant, the data in the James
18 article show that it can't be correct according to the
19 model that he has depicted here.
20 BY MS. RENZI:
21 Q So essentially Dr. Deth's reliance on the
22 data refutes that part of his hypothesis.
23 A That's correct. That aspect of his
24 hypothesis, according to the data that he has
25 presented, really cannot be.

1 The second point on this slide, and I have
2 also listed this, I've given you a separate slide on
3 this with a number two on it, but for this
4 illustration I'm just going to add this directly to
5 the Slide 19.
6 The second point that's very important is
7 that Dr. Deth relies upon an inhibition of cysteine
8 transport, the EAAT3, the inhibition of this step is
9 particularly critical in the mechanism.
10 So I think it's important to introduce the
11 discussion of the way the body maintains amino acid
12 supply, and so in Slide 22 I have illustrated this,
13 which would be sort of basic cell physiology.
14 The way the body works, the way the cells
15 work to make proteins, we are constantly making
16 proteins. It's the way our bodies have to make
17 proteins all the time.
18 The proteins require 20 amino acids. So the
19 question is, how does the cell avoid only having 19 of
20 those? You may have all 20 of them in the kidney, but
21 if you only have 19 of them in the liver you can't
22 synthesize proteins in the liver. So how does the
23 cell, how do all of the cells maintain, despite all
24 the variations in metabolism, how do the cells assure
25 that every cell always has all 20 amino acids so they

1 can continue business as usual?
2 The way they do that is that all cells have
3 multiple amino acid transporters. They don't just
4 have one transporter, they don't just have EAAT3.
5 They all have multiple transporters. Many of those
6 transporters have a characteristic, they're called
7 antiporters. The anti means, if you look at the
8 figure in Slide 22, the antiporter means that what
9 these transport systems do is they take one amino acid
10 on one side, amino acid one, and they exchange it for
11 amino acid two on the other side.
12 In other words, if you have a high
13 concentration of amino acid one on one side, it will
14 be going out of the cell. At that time it will be
15 driving another amino acid into the cell.
16 By having a series of these as illustrated
17 here, what this does is it assures that all amino
18 acids are balanced.
19 I have here on the top, amino acid two in a
20 slightly larger font. What that's meant to indicate
21 is that that's at a higher concentration. So if you
22 had a higher amount of that on that side, it would be
23 moving outside in exchange to bringing amino acid one
24 inside.
25 Now because you have other transporters here

1 at the bottom, amino acid one being exchanged for
2 amino acid three, what that means is as you increase
3 amino acid one it now is going to go out and bring in
4 amino acid three.
5 So by having a series of these it assures
6 that all 20 amino acids are maintained in a cell.
7 The important point with regard to this is
8 really shown in the next slide, Slide 23. This was
9 Dr. Deth's data. What these data show is that over a
10 very broad range of Thimerosal concentrations, that is
11 ten to the minus 12 to ten to the minus six, there's
12 really essentially no effect on the cysteine uptake.
13 What that's telling us is that yes, you have
14 this other transport system, cysteine transport is
15 going on anyway, even if this first point which we
16 don't really have the details, so we don't know
17 whether that is just some aberration of the experiment
18 or whether that's a real effect. But certainly these
19 data from ten to the minute twelve from ten to the
20 minus six are very consistent. There's really very
21 little effect there.
22 Now if one goes back to the absolute
23 concentrations and measures how much cysteine is being
24 taken up under those conditions? What you would see
25 if you calculated out the rates, and I haven't done

1 this on his experiment so I don't know exactly the
2 conditions. But based upon my knowledge of these
3 types of experiments in other cells, in other culture
4 conditions, this rate is substantially higher than the
5 rate that you would need for glutathione synthesis or
6 that you would need for protein synthesis.
7 In other words these conditions, what this
8 shows is that over this very broad range of Thimerosal
9 there is really not a sufficient inhibition of the
10 cysteine transfer for this aspect of the hypothesis to
11 really carry any weight.
12 My impression from that is, coming back to
13 Slide 19, is that this component of the hypothesis is
14 also incorrect. His data does not show you would have
15 a sufficient inhibition of the cysteine uptake to
16 actually have any effect on these downstream pathways
17 as he has argued.
18 Going on to, in terms of his model here,
19 this is back to Slide 19 or with already the annotated
20 Slide 24 where I have written number three at this
21 point on the diagram.
22 So there's a real question with regard to
23 Dr. Deth's argument as far as what determines whether
24 homocysteine goes through the degradative pathway or
25 whether homocysteine goes through the recycling

1 pathway of metabolism. So that's here by the
2 homocysteine, if it's going up that's the oxidated
3 pathway; if it's going down, that's the recycling
4 pathway.
5 Is that clear? I annotated this.
6 So the critical question now is what happens
7 to the homocysteine.
8 I'm getting the sense that I've lost you
9 all.
10 SPECIAL MASTER HASTINGS: On that particular
11 diagram I don't see the homocysteine.
12 THE WITNESS: That's HCY. This is Dr.
13 Deth's slide and his nomenclature, I apologize for
14 that. Let me write that on here. Homocysteine is
15 that right there.
16 A critical component of his argument is that
17 the glutathione which is at the top up here on this
18 diagram, that the glutathione is determining whether
19 homocysteine goes through the degradative pathway or
20 whether homocysteine is being recycled in the
21 methylation cycle. So that's a critical component of
22 his argument.
23 What we know about this from the literature
24 is that the degradative pathway is largely controlled
25 by the amount of methionine that we have in the diet.

1 So if we have excess methionine in the diet the system
2 works to stimulate that pathway to be able to degrade
3 the excess methionine. That's how we get rid of the
4 excess methionine.
5 So what we can see from this is that the
6 literature tells us that at the bottom of this that
7 methionine is an important determinant of that
8 degradative pathway.
9 Now the other literature that's very
10 important is that S-adenosylmethionine which is also
11 in this lower circle here, the methionine, the
12 methylation circle --
13 SPECIAL MASTER HASTINGS: And you just
14 circled the SAM.
15 THE WITNESS: SAM. That's S-
16 adenosylmethionine. Let me write that down here.
17 Now the S-adenosylmethionine is an important
18 regulator of two enzymes. One of those enzymes is the
19 sysdefining betasynthate, this enzyme that determines
20 whether homocysteine is degraded.
21 If this SAM, S-adenosylmethionine, this is
22 high, it stimulate that enzyme.
23 If it is high it inhibits this remethylation
24 from methyltetrahydrofolate.
25 So in effect what the literature shows is

1 that the control at step three is not from
2 glutathione, but rather from the components within
3 this methylation cycle, that is methionine and SAM.
4 BY MS. RENZI:
5 Q You found one more critical flaw in Dr.
6 Deth's hypothesis, is that correct?
7 A That's correct. I have summarized those
8 points on Slide 25. That's the points that I just
9 made.
10 Finally then, in terms of the, what I
11 consider critical flaws in these hypothesis, concerns
12 this step four here which is necessary to close the
13 cycle in terms of signaling. That has to do with the
14 methionine synthase reductase.
15 So in the data that Dr. Deth provided, this
16 is taken from Dr. Deth's Slide 39.
17 SPECIAL MASTER HASTINGS: You're on Slide 27
18 now?
19 THE WITNESS: Yes, my Slide 27. This is
20 data from Dr. Deth's slide which he had taken, quoting
21 Dr. James' article where he was showing the genetic
22 variations in support of his hypothesis.
23 What you can see from this, this is the
24 lower portion of that Table 3 from James' article, is
25 this reductase that's required for the methionine

1 synthase reductase, the MTRR.
2 What you can see from this data is that the
3 odds ratio is .78, .69, .61, and .66 for the different
4 genetic variations in this particular protein. This
5 particular gene.
6 Now what the odds ratio means is if the odds
7 ratio is greater than one, it means those variations
8 are associated with increased risk. If you notice in
9 the table, which I don't have here, but if you go back
10 to the table, the other variations that were in that
11 table had an odds ratio greater than one.
12 However, for this particular gene, the odds
13 ratio is less than one. That means these genetic
14 variations, if they're actually associated with
15 autism, are protective.
16 So if we go back to the mechanism that's
17 drawn in Dr. Deth's hypothesis, that's completely
18 inconsistent because instead of the genetic variation
19 at this step causing a problem, contributing to
20 autism, it's actually, according to the data, it's
21 protective. So to me this, it really says that at
22 four critical sites in the scheme, that the pieces
23 just don't fit together that that's a plausible
24 hypothesis and a plausible mechanism for changes
25 related to sulfur amino acid and as a cause of autism.

1 BY MS. RENZI:

2 Q The data that Dr. Deth presented in

3 formulating his hypothesis doesn't support his

4 hypothesis, is that correct?

5 A That's correct. These are the data that he

6 presented.

7 Q We'll go now to Slide 28.

8 A Slide 28 really is Dr. Deth's Slide 41,

9 going back to just his scheme on this.

10 What I think the data show, to me fairly

11 clearly, there really is not appropriate evidence,

12 this is just not the data saying that the dose of

13 Thimerosal is enough to alter the sulfur metabolism.

14 This is really not established by the data.

15 Similarly, if you had a perturbation in the

16 sulfur, even if a very minor effect happened, it

17 really would not be at a magnitude that one could

18 consider that that was responsible for oxidative

19 stress. I think you have to conclude that this is not

20 established either, the second point.

21 Finally then, if you look at the subsequent

22 aspects of that, the variation, the oxidative stress,

23 there's a normal variation in oxidative stress and the

24 magnitude of effects are really not appropriate, and

25 in fact the mechanisms that he's drawn cannot account

1 for changes in the methionine synthase activity in the
2 in vitro data that he provided without in vivo data
3 supporting it. Really you have to conclude that this
4 step in the pathway is also not established. That is
5 the oxidated stress to the methionine synthase.
6 From that summary, from my standpoint there
7 really is no plausibility to this hypothesis at all.
8 It's what I would consider a scaffold without a
9 building. There are a lot of components to it but it
10 doesn't have the strength, the solidity of being solid
11 science and being reasonable or plausible.
12 I have just a few summary comments if you
13 want me to go through those.
14 This is my final slide, Slide 29. I think
15 in terms of my overall consideration of this, I think
16 point one is that the cumulative dose of Thimerosal is
17 too low because of the magnitude of effects on
18 glutathione metabolism that would be required to
19 conclude there's any likelihood of effect there.
20 That's just not plausible.
21 The natural variation, point two, the
22 natural variations in the glutathione are greater than
23 what one would expect from the low dose of Thimerosal
24 that are present in Thimerosal-containing vaccines.
25 The third point is that at the low, if you

1 did have an effect, you would have to conclude that
2 the low non-toxic dose would probably be protective,
3 because that would be activating protective mechanisms
4 that ubiquitously occur.
5 The fourth, the in vitro studies show that
6 the Thimerosal disruption of metabolism is probably
7 occurring under non-specific conditions, ones where
8 you simply have the cellular conditions set up so
9 you're going to be disrupting lots of things and
10 they're not going to be giving any specificity.
11 That's simply because they're at irrelevant
12 concentrations, irrelevant amounts.
13 I have to conclude that the data really
14 don't support this hypothesis that there is an effect
15 no the glutathione system that's causing oxidative
16 stress and that's a cause of the autism.
17 MS. RENZI: Thank you.
18 SPECIAL MASTER VOWELL: Are you prepared to
19 begin Cross-Examination or would this be a good time
20 for our mid-morning break?
21 MR. WILLIAMS: I would very much enjoy a
22 break if that would be all right with you.
23 SPECIAL MASTER VOWELL: All right
24 I have 10:40 by my clock. Special Master
25 Hastings' watch is agreeing with me. So why don't we

1 come back at five minutes to 11:00.
2 MR. WILLIAMS: Thank you.
3 (Whereupon, a recess was taken).
4 SPECIAL MASTER VOWELL: All right, we're
5 back on the record.
6 Mr. Williams, are you prepared to begin your
7 Cross-Examination of Dr. Jones?
8 MR. WILLIAMS: Thank you.
9 SPECIAL MASTER VOWELL: You may do so.
10 CROSS-EXAMINATION
11 BY MR. WILLIAMS:
12 Q Good morning, Dr. Jones.
13 A Good morning.
14 Q I'm Mike Williams here for the Petitioner
15 steering committee and these two children.
16 I want to start by asking you about a paper
17 you published on mercury toxicity. I have an extra
18 copy of it here for you and one for the counsel.
19 This wasn't mentioned in your Direct
20 testimony but this is off your CV and you're probably
21 familiar with this paper.
22 A Yes.
23 Q Let's show the title, please.
24 The title says, "Differential oxidation" and
25 you tell me how to pronounce it. I don't know whether

1 it's thio or theo.
2 A Thio.
3 Q Thioredoxin?
4 A Yes.
5 Q "Thioredoxin-1, thioredoxin-2, and
6 glutathione by metal ions."
7 A Yes.
8 Q You've published quite a few papers on
9 thioredoxin, haven't you?
10 A Yes.
11 Q What is thioredoxin and what is its
12 significance in the, if we can concentrate on what the
13 significance would be in the brain that would be a
14 good thing.
15 A I can't really concentrate on that. We have
16 studied, we study mostly cellular mechanisms. These
17 are studies to try to understand the functions of the
18 thio-disulfide systems in cells. This particular
19 paper was looking at thioredoxin-1 which is a
20 cytoplasmic and nuclear form of this antioxidant
21 protein, and thioredoxin-2 which is the mitochondrial
22 form of this protein. Then looking at that in
23 relative to the changes in glutathione within the
24 cell.
25 Q How do thioredoxins in either the cell or in

1 mitochondria relate to glutathione?
2 A They are sort of a complementary system.
3 One of the points with regard to the function of
4 glutathione and its role as an antioxidant is that
5 glutathione is not alone. There are many different
6 antioxidant systems and that also is part of the
7 questioning with regard to the term glutathione.
8 There are many other protective systems in the cell
9 and thioredoxins are one of these widely distributed,
10 protected systems.
11 Q This is one of your original research
12 papers, right?
13 A That's correct.
14 Q I know you looked at a number of metal ions,
15 but one of them was HG++ or mercuric mercury, correct?
16 A Yes, that's correct.
17 Q Why did you look at HG++ and the
18 thioredoxins?
19 A The reason for that is that we were looking
20 at different metals to see whether or not some metals
21 affected the thioredoxin systems differently than they
22 affected the glutathione system. Really a comparative
23 type of study.
24 Q I couldn't find any funding source for this
25 study. Is this just --

1 A This was funded, this may have been one
2 where we did not cite this. It was funded from my NIH
3 grant on the, I have a nuclear thioredoxin where I've
4 been studying the functions of the glutathione and the
5 different subcellular compartments. So this was
6 funded by that NIH grant. It would have just been an
7 oversight if we didn't cite that on this.
8 Q If mercury, if HG++ were able to
9 significantly inhibit these two enzymes, thioredoxin-1
10 or 2, would that be a sign that it could be toxic to
11 cells?
12 A Certainly. The concentrations we used were
13 ten to 100 micromolar which are obviously very high
14 concentrations. But what the data showed was that you
15 can in fat change the function of the thioredoxin by
16 putting in mercury.
17 Q This is in both cells and in mitochondria.
18 If you have enough mercury there to suppress this or
19 to inhibit this enzyme, would that happen in both
20 mitochondria and in the cell itself?
21 A It would happen wherever the mercury
22 accumulated, yes. That's what the data showed in this
23 paper.
24 It bears the same point as I've already
25 brought out. When you use these cell culture studies,

1 we were not addressing in vivo relevance of the
2 specific dosing. What we were asking in this study
3 was just something that had not been addressed before.
4 That is scientifically, does the thioredoxin system
5 respond in the same way as the glutathione system.
6 The answer to that data is clearly no. They respond
7 differently.
8 Q If we could turn to -- by the way, we marked
9 this as Trial Exhibit 6 for the Petitioner. It's not
10 on our master reference list yet.
11 (The document referred to was
12 identified as Petitioner's
13 Trial Exhibit 6.)
14 Q If you could turn to the second page of this
15 paper. In the left hand column there's a paragraph
16 that starts, "Discrimination between oxidation". Blow
17 up that paragraph, if you would.
18 It may take a little while to go through
19 this but I think this is going to be relevant, so bear
20 with me.
21 You're talking here about discrimination
22 between oxidation of the glutathione that's reduced
23 versus the oxidized glutathione, right? The GSH/GSSG?
24 A Yes.
25 Q And the TRX systems. TRX refers to

1 thioredoxin?

2 A Yes.

3 Q Both types.

4 A When I use it there, when we use it without

5 either one or two, yes, it's a general. This is a

6 protein that's found in most organisms and there are

7 different forms of it. So it has a conserved

8 functional active site. Whatever proteins have that

9 conserved active site, those are called thioredoxins,

10 yes.

11 Q And these would be in brain cells too,

12 right?

13 A Yes.

14 Q And you say that that discrimination between

15 how oxidation of the glutathione system and the

16 thioredoxin system could be very informative in terms

17 of mechanisms of toxicity.

18 Why can they be informative about mechanisms

19 of toxicity?

20 A Because the systems, we have multiple

21 protective systems basically. So one way to think

22 about systems such as oxidative stress is to think

23 about them just in terms of a global balance, a global

24 imbalance if you will of a pro-oxidant and an

25 antioxidant system.

1 Another way is to try to refine that so that
2 you now begin to look at how individual biochemical
3 systems work where you have these complementary
4 systems that work together to provide the protective
5 mechanism.
6 Q If a toxin, one of these metals or some
7 other toxin, could inhibit the thioredoxin system in
8 the mitochondria but it didn't affect the glutathione,
9 would that mean it was probably harmless because the
10 glutathione just rebalanced itself out?
11 A The systems are complementary. What that
12 means is that if you effect one of the systems the
13 other system takes over. So in terms of the
14 sensitivity, they oftentimes have a difference in
15 sensitivity and that's what we were looking at here,
16 is trying to begin to understand how those systems
17 differ in their sensitivity.
18 Q You were trying to see if there was a way to
19 discriminate with the effect of the metals on these
20 different systems.
21 A That's right.
22 Q If you had a significant inhibition of the
23 thioredoxin, would that be harmless because of
24 compensatory mechanisms?
25 A I can't really answer that question

1 directly, but what I will say is that there are drugs
2 that have been developed that are used at least in a
3 phase two initial clinical trials, targeting
4 thioredoxin with the goal to try to, and used in anti-
5 cancer therapy, to try to target and kill the cancer
6 cells by specifically inactivating the thioredoxin
7 system. So that concept is out there in the
8 scientific literature, yes.
9 Q The concept that you could have a toxic
10 effect just by affecting the thioredoxin system.
11 A Yes, if you could find something that would
12 do that.
13 Q Let's go on in this paragraph. You say,
14 "For instance the activation in nuclear translocation
15 of the transcriptant factor Nrf-2."
16 Now you had Nrf-2 on one of your slides
17 today and you didn't explain what it would. Would you
18 please explain what it is now?
19 A What that mechanism does, if you have
20 something that alters that response, so if you have
21 something that gives you a low level of oxidation or a
22 low level of challenge to the cell that would
23 potentially perturb the glutathione system, what that
24 does is that turns on this Nrf-2 system. By turning
25 on this Nrf-2 system it causes an increase in the

1 thioredoxin. So it not only improves your glutathione
2 system but it improves your thioredoxin system.
3 So that's really the point of this, that
4 both of these systems are responding together. It's
5 not like you have one system or the other system.
6 They both are being controlled, and as you turn on
7 that protective mechanism it enhances your protection
8 for both the thioredoxin and the glutathione.
9 Q You conclude this paragraph by saying "If
10 metals activate apoptosis" is that how you say that?
11 A Apoptosis.
12 Q The second P is silent because of the Greek
13 background of some kind.
14 A Yeah.
15 Q "If metals activate apoptosis via ASK1", and
16 ASK1 is another mechanism for gene activation here?
17 A No. ASK1 is apoptosis signal-regulating
18 kinase one.
19 Q Another enzyme.
20 A You don't need that. ASK1 is good enough.
21 It's an enzyme that is a kinase, it's a
22 phosphorylating enzyme that can activate a death
23 program, a cell death program.
24 Q That's the concept behind these cancer
25 therapies they're working on, to try to kill cancer

1 cells this way?

2 A What happens is the cancer cells have a

3 change in expression of a lot of these different

4 enzymes and the way that they protect themselves is by

5 giving, by having a very large change in certain of

6 these enzymes, so it's a mechanism for controlling the

7 cell death.

8 Q If we turn to page 142 of the paper, it's

9 the one that has Figure 2 on it. It starts the

10 discussion section.

11 Let me start with the paragraph in the right

12 hand column bottom that says "in contrast".

13 You found in this study that mercury had

14 different effects on these enzymes than some of the

15 other metals, right?

16 A That's correct.

17 Q What did mercury affect, in your study? And

18 we're talking again about mercuric mercury, HG++.

19 A At ten micromolar and at 100 micromolar

20 mercury when added to these cells, they caused a

21 change in the thioredoxins and an activation of the

22 apoptosis, the ASK1 mechanism.

23 Q And you say in contrast to these metals,

24 and you were referring to copper, iron and nickel I

25 think when you say these metals, right?

1 A Yes.

2 Q You found that arsenic, cadmium and mercury

3 oxidized both of those thioredoxin enzymes, correct?

4 A Yes.

5 Q But they had little effect on the

6 glutathione cycle.

7 A Right.

8 Q And they did induce cell toxicity after 24

9 hours.

10 Now we've heard that you have to do these in

11 vitro studies long enough to see the end point. Do

12 you think that was long enough?

13 A It was at a high enough dose.

14 Q But time wise I'm talking.

15 A In general, these are, it really varies

16 depending on the cell type. For instance some cells

17 don't even have enough ASK1 that they would even show

18 this effect at all. This gets at the point of having,

19 these are not normal cells. When you take a cell line

20 like this and put them in culture we really, this is

21 one of those issues where you take a/c ell line that

22 does show a response under the conditions that you

23 want to see an effect.

24 So what we were doing here, we had a system

25 where we knew we could kill the cells under these

1 conditions and we wanted to see under those conditions
2 where we were killing the cells, what the effect was
3 on the thioredoxin and the glutathione system.
4 Q I know you only went down to ten micromolar
5 here.
6 A We just did two conditions, yes.
7 Q Do you know whether if you used one
8 micromolar of HG++ what you would have got here?
9 A The experiment was actually designed by
10 Jason Hansen. But Jason took this from the literature
11 and in his analysis we needed ten micromolar in order
12 to kill these cells. That was why that was selected.
13 Q Before the cell dies in this system,
14 wouldn't it become dysfunctional for a few of those
15 hours?
16 A We didn't really study anything else. We
17 were specifically interested in the question of can we
18 see a change in the thioredoxin and how does that
19 compare to a change in glutathione in the study. That
20 was really what the study was directed to do.
21 Q So you were looking for cell death as the
22 end point of the study, not some dysfunction of the
23 cell.
24 A Right. We were looking at cell death in the
25 study.

1 Q Isn't it reasonable to think, though, that a
2 lower dose might cause dysfunction before it caused
3 death?
4 A I can't speculate on this at all because the
5 experiment was designed with an outcome to study and
6 we studied that outcome. Scientists set up hypotheses
7 to test hypotheses, and this was testing the
8 hypothesis.
9 Q Let's go to a couple more of your findings.
10 If we turn the page and go to the left hand
11 column, this is now page 143.
12 You discovered a difference between the
13 effect in mitochondria in the cell itself here, didn't
14 you?
15 A In the difference between --
16 Q If you highlight the first sentence of the
17 first paragraph on the left side, and blow it up.
18 This says that the greater extent of
19 oxidation of thioredoxin 2 compared to thioredoxin 1
20 indicates that mercury has greater oxidative effects
21 on the mitochondrial compartment than the cytoplasmic
22 compartment. Have I understood that correctly?
23 A Yes, you understood that correctly. That is
24 what the data show, that the mitochondrial thioredoxin
25 -- If you look at the chemical characteristics of that

1 protein, that protein is a bit different than the
2 cytoplasmic form of the protein, and that protein
3 shows more oxidation under these conditions than the
4 cytoplasmic.
5 Q And oxidation is, in this instance, it's bad
6 for the cell, it might be good for the cancer patient.
7 A It's not really, that is a question that we
8 really don't know at present. Science hasn't
9 established to what extent a natural variation in
10 thioredoxin occurs.
11 For instance when we look at other cells in
12 culture, actually even in human biopsies that we've
13 measured, where we measured thioredoxin 2 and
14 thioredoxin 1. Just taking a normal human colon
15 biopsy or ileal biopsy and measuring their redox
16 state, it's under normal healthy conditions it's more
17 oxidized than these conditions that we're seeing here
18 under the toxic conditions.
19 I don't think we know enough to be able to
20 answer that question. I can see why you would want to
21 speculate on that, but the data is not there. I don't
22 think we can make that conclusion.
23 Q Was the effect of HG++ on both thioredoxins
24 enough to kill the cell?
25 A In this particular model we don't even

1 really know that. All we know is these cells under
2 these conditions with a high amount of mercury died.
3 We don't have any experiments that actually rigorously
4 say that that is the cause of death in these cells.
5 There's no way, that's just a correlation at this
6 point. We put in that amount of mercury, we saw these
7 changes, and we saw these cells die.
8 I can see why you would want to extend that
9 into a logical argument, but it really isn't a logical
10 argument. It's just an association at that point.
11 There's no causal. You can say the mercury caused the
12 cells to die, but you can't say that the mercury
13 caused the cells to die by the change specifically in
14 the thioredoxin.
15 Q Why does NIH want to spend its precious
16 dollars on this kind of stuff?
17 A Well, because we are the pioneers in the
18 methods to be able to discriminate the different sub-
19 cellular compartments and how they are regulated.
20 There really isn't very much understanding of how the
21 different compartments are regulated.
22 Q Finally here, if we turn to page 144 of the
23 study, Figure 4. This is where you showed the
24 relative effect of the different metal ions.
25 Blow up Figure 4, Scott.

1 There are three of them that are
2 particularly high, and the one on the right, the third
3 one, that is the mercury, HG++, right?
4 A Yes.
5 Q And you are measuring what in this, this is
6 the -- What is the vertical axis here?
7 A Again, these are at 100 micromolar mercury,
8 so this is a horrendously high concentration. But
9 this is an indirect assay of the ASK1 activity. The
10 apoptosis signal-regulating kinase 1 activity. So
11 this is one of the multiple cell death activating
12 pathways.
13 What this shows is that under these
14 conditions that these three metals are ones that give
15 more of an activation of that enzyme.
16 Q You've made a point all morning and in your
17 report that although we see these toxic effects of
18 HG++ on these cell enzymes, the dose is so high that
19 it's probably not relevant here. I think the
20 testimony has been, I think both sides have agreed
21 that the nanom overdoes of HG++ in those infant monkey
22 brains was around 30 nanomolar on average. Is that
23 approximately your understanding?
24 A I would have to go back and look at the
25 original paper on that. But I know it was a very low

1 amount, yes.
2 Q And by the way, in your report you do say
3 the Burbacher paper, let me show this on page 13 of
4 your report.
5 You make a comment about the Burbacher
6 paper. Page 13.
7 It's right in the middle of the last big
8 paragraph, "The primate model of Burbacher". If you
9 can blow that up and highlight that sentence. "The
10 primate mode of Burbacher."
11 So you said in your report that "The primate
12 model of Burbacher et al, 2005," that is talking about
13 that infant monkey study, right?
14 A This was the Burbacher paper, yes.
15 Q You say it showed clear evidence for
16 delivery of mercury to the brain following injection.
17 A I don't see there's any way that you could
18 avoid that conclusion. That's what the data show.
19 Q But again, it was delivered at a dose
20 significantly lower than what you've measured and what
21 you were talking about this morning.
22 A There's a difference between being able to
23 detect something and then having a concentration
24 that's relevant to the in vitro studies.
25 So the ability to detect has to do with the

1 sensitivity. If you take, for instance, I have a
2 colleague who works at Georgia Tech who's developed
3 one of these sensors, these electrical noses that they
4 use for sensing cocaine. He says you can pull a $20
5 bill out of anybody's wallet, that has a $20 bill, and
6 that these instruments are sensitive enough to detect
7 that cocaine.
8 So what it says is the ability to detect
9 something at very low levels, that's not really the
10 relevant question. The relevant question is how much.
11 Q I understand that.
12 I want to ask you a little bit about your
13 background. you spent quite a bit of time at the
14 Karolinska Institute in Sweden, haven't you?
15 A Yes.
16 Q How many times have you been over there?
17 Let's start first where you went there to
18 study your work or do research.
19 A I was there in '77 and '78. I was back in
20 either 1980 or '81, probably again in either '82 or
21 '83. I was back again in probably '87. I think I was
22 back in '94 and probably back in '97, for different
23 varying periods of time doing research.
24 Q You may know how to pronounce Marie Vahter's
25 name. So you know who Marie Vahter is?

1 A No, I don't know Marie Vahter.
2 Q She's an author on the adult monkey studies
3 from the Karolinski Institute.
4 You do know Arne Holmgren, don't you?
5 A I know Arne, yes.
6 Q How long have you know him?
7 A Perhaps 30 years.
8 Q You've published at least a couple of
9 chapters in books that he's edited?
10 A Yes.
11 Q You respect his work?
12 A Absolutely. He's one of the best.
13 Q Do you have a way of tracking, PubMed or any
14 other system, when your papers get cited? For
15 example, the paper we've just been talking about, the
16 --
17 A I really don't spend my time at that. I
18 spend my time on original research.
19 A I wanted to see if this thioredoxin paper
20 had been cited by anybody, and we found one by
21 Holmgren that actually discusses your paper, so I want
22 to show that to you.
23 This will be our Trial Exhibit 7.
24 //
25 //

1 (The document referred to was
2 identified as Petitioner's
3 Trial Exhibit 7.)
4 Q If you could blow that up, Scott, and show
5 the title, please?
6 This is about the same thioredoxin system
7 that you were studying in your paper, right?
8 A Yes, he studies thioredoxin.
9 Q And this is the Karolinski Institute, and
10 Dr. Holmgren has done this study.
11 A It's very possible that it was not done in
12 Stockholm, but I don't know from this.
13 Q We've highlighted. The very last part of --
14 A -- by Swedish, yes. Okay.
15 Q You give me that?
16 A Yes.
17 He's definitely at Karolinska.
18 Q We're going to take a little bit of time to
19 go through this because this is a study of HG++
20 effects on thioredoxin. You haven't seen this paper
21 before, I take it?
22 A No, I haven't. I would really need time to
23 study it for me to be able to comment on it at all.
24 Q And I understand that you may not be able to
25 give your interpretation of it today, but I want to

1 focus on what dose they used eventually and I want to
2 take the time to put that in context.
3 So if I ask you a question you can't answer
4 because you haven't read the whole paper yet, that's
5 okay, but let's do the best we can. I only came
6 across this paper last night myself.
7 It does cite two of your papers in the
8 bibliography, by the way, including the one we just
9 talked about.
10 If you could blow up the first half of the
11 asterisked stuff.
12 It says that mercury toxicity mediated by
13 different forms of mercury is a major health problem,
14 however the molecular mechanisms underlying the
15 toxicity remain elusive. We analyzed the effects of
16 mercury chloride and monyl methyl mercury.
17 By the way, when they study mercury
18 chloride, they're doing that so they can deliver HG++
19 to the system they're testing, right?
20 When they study mercury chloride, they're
21 using that to deliver HG++, that ion to the system --
22 A That is what you're adding, yes. You are
23 adding HG++ because the chloride will be released once
24 it goes into the solution. Yes.
25 Q On the proteins of the mammalian thioredoxin

1 system. You said this thioredoxin system was
2 conserved evolutionarily so that most mammals relied
3 on the system for cellular function. Right?
4 A Yes.
5 Q They looked also at something called
6 thioredoxin reductase, TrxR. We already learned that
7 Trx is short for thioredoxin. W hat is thioredoxin
8 reductase?
9 A Thioredoxin recluctase is a group of enzymes
10 that reduce thioredoxin.
11 Q That's also an important function in the
12 cell?
13 A they have an important function in the cell,
14 yes.
15 Q They looked at glutaredoxin, glutathiol
16 reductase and gloucaral redoxin. Are those also
17 important enzymes in the cell?
18 A Yes, they are.
19 Q What they say here was that mercury chloride
20 inhibited recombinant thioredoxin reductase with an
21 IC50 value of 7.2 and 19.7 nanomolars respectively.
22 Do you see that?
23 A Yes.
24 Q Do you want me to comment on that?
25 A Yes. I haven't read this paper, but it's

1 obvious that you don't understand the science behind
2 this. When you do this type of an experiment you're
3 taking a pure protein where there is completely no
4 other thiols at all.
5 There are 214,000 different thiols encoded
6 in the human genome. So what you've done is you
7 removed in this case over 210,000 of those and you've
8 taken only the remaining two to five thiols that are
9 left in a single protein. So now you don't have the
10 other 200,000 thiols that would be interacting.
11 So when you're doing your calculations
12 relative to this single protein with this single thiol
13 it's just a pure system. It doesn't have really any
14 relationship to the way those react in the context of
15 the entire cell or in terms of the context of the
16 entire organism. I think that's very important to
17 understand that you can't just take a pure protein and
18 look at the concentration that interacts with it, and
19 be able to, it's even worse than taking the cell
20 culture and extrapolating, to take a single protein
21 and try then to extrapolate. That's doesn't fall into
22 the realm of good science.
23 Q Let's see what Dr. Holmgren said at the
24 bottom of this abstract then we'll go through the
25 paper a little bit.

1 The sentence at the very end of the abstract
2 that says "overall", Scott.
3 Dr. Holmgren and his scientists say that,
4 "Overall, mercury inhibition was selective toward the
5 thioredoxin system. In particular the remarkable
6 potency of the mercury compounds to bind to the
7 selenol-thiol in the active side of thioredoxin
8 reductase should be a major molecular mechanism of
9 mercury toxicity."
10 I take it from your earlier comments just
11 now that you don't agree that that is a way to
12 interpret that.
13 A I think what you have to understand is that
14 Dr. Holmgren is a biochemist, he works with purified
15 protein, and as far as the pure chemistry of the
16 interaction with the purified protein, he has studied
17 that and he does a first rate job of that.
18 As far as I know he does not do, he does
19 some cell cultured work. He has not done any in vivo
20 toxicity work at all. He's not trained as a
21 toxicologist. He's really studying biochemical
22 mechanisms.
23 Your first phrase that you read from this
24 paper, and I don't know that we can really go beyond
25 that, but your first phrase that the molecular

1 mechanism, and these are mechanism based studies.
2 They're trying to understand the chemical mechanisms
3 of how these proteins work. To do that you purify the
4 protein, you try to understand the pure protein. But
5 then to be able to understand it in a toxicologic
6 sense you really have to put that back into the
7 context of the whole organism. I think that's my
8 point.
9 I don't know, you can ask me more questions
10 on this. I haven't read it. But my feeling is that
11 you're really going after something that's irrelevant
12 to the human exposure when you start trying to
13 extrapolate from something that is even worse than a
14 cell study. It's a purified protein study.
15 Q If we turn to the second page of this paper
16 which is in the journal at page 11914, it's the first
17 full paragraph, Scott. The first sentence there says
18 that the Trx system is critical for cellular stress
19 response, protein repair, and protection against
20 oxidative damage.
21 Do you agree with that statement?
22 A It is an important system in the body. Yes.
23 That is an important system in the cell.
24 Q Is there some part of this sentence you
25 don't agree with?

1 A No, I'm just a slow reader.
2 Q If we now turn to page 11916 of this paper,
3 I want to concentrate on Figure 1 here, just to look
4 at the doses of both methyl and inorganic mercury.
5 This is their graph, similar to the graphs
6 we've seen from Dr. Deth, that shows the relative
7 activity of both HG++ and methyl mercury in nanomolar
8 concentration on the inhibition of thioredoxin
9 reductase. Have I interpreted that correctly?
10 A I haven't had a chance to really review this
11 so I can't say.
12 Q Can you at least interpret, when it says
13 concentration in nanomolar across the bottom, can you
14 at least --
15 A Was this a purified protein? Was this a
16 study on a purified protein?
17 Q We're going to have experts to talk about
18 this. I can't testify here unfortunately.
19 A If I don't have time to read the paper, if
20 you're just giving it to me right now, how do you
21 expect for me to try to comment on it?
22 Q All I'm going to ask you now is about what
23 the bottom numbers mean on these graphs. Aren't those
24 nanomolar concentration?
25 A You can read as well as I can read, sir.

1 Q Does it say concentration of nanomolar below
2 that graph?
3 A On the graph that you're showing me yes,
4 that's what it shows. And did you answer my question?
5 Is this a purified protein? Because I've already said
6 that if it's a purified protein it's completely
7 irrelevant to make that type of a comparison to
8 nanomolar concentrations that you would see in vivo.
9 From my standpoint -- Well, I'm sorry.
10 SPECIAL MASTER HASTINGS: Can you just
11 answer his question?
12 THE WITNESS: I'm sorry, I'm irritated by
13 that, so I'm sorry.
14 SPECIAL MASTER VOWELL: Can you answer his
15 question though, if he asks you another one?
16 THE WITNESS: Yes. Okay.
17 BY MR. WILLIAMS:
18 Q I think the answer is, and we're going to
19 see the answer, is that they also looked at cells in
20 this study. Whole cells. Not just isolated proteins.
21 If we turn to page 11918.
22 MR. MATANOSKI: At this time, Your Honor,
23 I'm going to have to object. If we're going to go
24 through an article, our witness just said he has not
25 had time to read this article. I suppose he can

1 comment whether at the bottom of a graph what the X
2 axis is or what the Y axis is. But if he's going to be
3 commenting on the substance of this article he needs
4 time to review it.
5 Now this article was published, it looked
6 like it was published in March of 2008. The
7 opposition has known who our witnesses were since,
8 well at least, well they've actually had their report
9 since February. If they were going to cross-examine
10 our witness on the substance of an article that has
11 been out for over two months now we should have had
12 notice so that our witness could read it ad properly
13 prepare to answer questions on it.
14 SPECIAL MASTER VOWELL: Mr. Williams?
15 MR. WILLIAMS: If we'd had this last week we
16 would have used it. Last night I started looking at
17 his CV. We --
18 SPECIAL MASTER VOWELL: But you had his CV.
19 MR. WILLIAMS: We had his CV. We did. And
20 this is dated May 2nd. We literally didn't find this
21 until last night.
22 SPECIAL MASTER VOWELL: We can proceed to
23 ask questions about it, Mr. Williams, but if you're
24 going to get answers that I don't know, I haven't read
25 the article, it's not particularly helpful to the

1 three of us sitting up here. Again, that's your
2 audience.
3 MR. MATANOSKI: Actually it says, papers in
4 press March 4th. I know it says May 2nd on the bottom
5 of the volume, but it apparently was available two
6 months ago.
7 BY MR. WILLIAMS:
8 Q Let me just ask then, you were making a big
9 point about isolated protein, so let me just make this
10 point and then I'll drop it.
11 If we turn to the last page of this paper,
12 the text, 11922, and we look in the right hand column,
13 right in the middle of that paragraph, Scott, it says,
14 "We have demonstrated". "We have demonstrated that in
15 a cellular system the inorganic form of mercury
16 preferentially targets the thioredoxin system of which
17 thioredoxin reductase was inhibited to a greater
18 extent than thioredoxin itself by more potent mercury
19 concentrations."
20 So they weren't studying just isolated
21 proteins here were they, doctor?
22 A I have not looked at the data. I have not
23 read this paper.
24 Q Thank you.
25 What function do mitochondria play in a

1 cell?

2 A Mitochondria are the major energy source in

3 the cell. The major supplier of ATP, the major energy

4 currency of cells.

5 Q You have published a lot on mitochondria

6 over your 30 years, haven't you?

7 A That's correct.

8 Q You've chaired symposia on mitochondria?

9 A Yes.

10 Q You're probably one of the world's leading

11 experts on mitochondria, isn't that fair to say?

12 A I have expertise in mitochondria, yes.

13 Q I want to show Petitioner's Master Reference

14 71, which is the case report on a child with

15 mitochondrial dysfunction in autism.

16 MR. MATANOSKI: We're going to object now

17 because I'm thinking we're going to get to Theory 2C

18 at this point. I'm not sure I've seen anything

19 referenced in Dr. Deth's expert report about an effect

20 of Thimerosal on mitochondrial function.

21 SPECIAL MASTER VOWELL: Let's see where

22 we're going to go with it.

23 BY MR. WILLIAMS:

24 Q Let me give the Doctor a copy of the paper

25 first.

1 Did the DOJ lawyers ever show you that paper
2 while you were preparing for today?
3 A I have not, I focused on sulfur. My
4 expertise is on sulfur metabolism. My expertise on
5 oxidative stress. I did not address any questions
6 related to potential involvement of mitochondria, and
7 I have not seen this paper.
8 MR. WILLIAMS: Then I won't ask you anything
9 more about that, and that's all I have for you. Thank
10 you.
11 SPECIAL MASTER VOWELL: Redirect?
12 MS. RENZI: No, thank you.
13 SPECIAL MASTER VOWELL: Do we have other
14 questions from my colleagues?
15 I'm going to ask one brief question, at
16 least I hope it will be brief, Dr. Jones.
17 You included on your Slide 20 a Table of
18 Results from the James study involving various
19 transmethylation and transsulfuration metabolites?
20 THE WITNESS: Yes.
21 SPECIAL MASTER VOWELL: You highlighted
22 cysteinylglycine. You did not comment or make any
23 comment on those levels that Dr. James found were far
24 lower in autistics than in the control sample. Do
25 those have any bearing on anything you've said?

1 THE WITNESS: The most difficult aspect of
2 this type of a comparison is that there are, in almost
3 every disease population that we have studied, the
4 glutathione levels are different from controls.
5 SPECIAL MASTER VOWELL: So anyone with any
6 disease.
7 THE WITNESS: Pretty much. If you go
8 through cardiovascular disease, diabetes, renal
9 disease, liver disease, lung disease. There are many
10 of these. There are general differences, and most
11 commonly there are decreases in glutathione.
12 SPECIAL MASTER VOWELL: So a reduced
13 glutathione level would seem then to be a response to
14 a disease process rather than a specific disease.
15 THE WITNESS: Right. It seems to be more of
16 a response to disease rather than a cause in terms of
17 the way I would interpret this. It's a very common,
18 it's a common consequence of different diseases that
19 we have studied.
20 SPECIAL MASTER VOWELL: That answers my
21 question.
22 Thank you very much.
23 Questions from either side based on mine?
24 (Witness excused).
25 All right, we're at about 11:40, which

1 appears to be early for a lunch break but Justice,
2 what's your thought on that? Do you want to put on
3 your next witness and at least begin before we start
4 our lunch break?
5 You need a consultation. I understand
6 that's fine.
7 MR. MATANOSKI: We would like to get
8 started, ma'am.
9 SPECIAL MASTER VOWELL: Great.
10 We'll just recess in place while you do the
11 changing of the guard here.
12 MR. MATANOSKI: Yes, ma'am.
13 SPECIAL MASTER VOWELL: We'll do a recess in
14 place then.
15 (Pause).
16 MR. MATANOSKI: We need about five minuets
17 to get set up, apparently.
18 SPECIAL MASTER VOWELL: Okay. Let's just
19 take a complete recess then. Be back in five minutes.
20 If you need more time, let me know.
21 (Whereupon, a brief recess was taken.)
22 SPECIAL MASTER VOWELL: We're back on the
23 record. We have Dr. Kemper on the stand.
24 Doctor, if you would raise your right hand.
25 //

1 Whereupon,
2 THOMAS L. KEMPER
3 having been duly sworn, was called as a
4 witness and was examined and testified as follows:
5 SPECIAL MASTER VOWELL: All right, Mr.
6 Johnson, you may proceed.
7 This is going to be Respondent's Trial
8 Exhibit, well, we don't have your 10 yet, so in case
9 we don't get it let's make this 10 and you can refer
10 to the next one as 11.
11 MR. JOHNSON: Yes, ma'am.
12 SPECIAL MASTER VOWELL: Okay.
13 (The document referred to was
14 identified as Respondent's
15 Trial Exhibit 10.)
16 DIRECT EXAMINATION
17 BY MR. JOHNSON:
18 Q Hello, Dr. Kemper. Could you please state
19 your name for the record please?
20 A Thomas Kemper.
21 Q Dr. Kemper, briefly describe your
22 educational background and employment history.
23 A My undergraduate degree was at Northwestern
24 University in 1954. Then the next four years were the
25 University of Illinois School of Medicine. After that

1 I was three years in residency training in Internal
2 Medicine in Neurology, moving at that point from
3 Chicago to Boston. After that I was a Fellow in
4 neuropathology at the Harvard Neurological Unit, the
5 Boston City Hospital, with Derick Denny Brown. The
6 next two years I was with Ray Adams, Massachusetts
7 General Hospital, also in neuropathology.
8 Following that I spent most of my time at
9 the Warren Anatomical Museum at the Harvard Medical
10 School with Dick Sigmund and Paul Yakoblev.
11 In 1975 I joined the neurological unit at
12 the Boston City Hospital as a neuropathologist where I
13 remained as an active neuropathologist until about
14 five or six or seven years ago. Now I'm in the
15 Department of Anatomy of Neurobiology at the Boston
16 University School of Medicine where I'm a professor in
17 that department in pathology and in neurology.
18 Q When again did you join Boston University
19 School of Medicine? What year?
20 A I think it was, I'll see it right here. It
21 was 1975.
22 Q So you've been on the faculty there for a
23 little over 30 years?
24 A That's correct.
25 Q Tell me again, what position do you

1 currently hold there?

2 A Well, I'm a full professor in the

3 Departments of Anatomy and Neurobiology, in Neurology

4 and in Pathology.

5 Q Is that three different departments?

6 A It's three different departments.

7 Q Dr. Kemper, do you consider yourself

8 primarily a research scientist?

9 A Yes, I do.

10 Q But I believe you mentioned you are also a

11 medical doctor. as well.

12 A Yes, I do. I also saw patients for a long

13 period of time.

14 Q As a professor, I take it that you teach

15 students?

16 A Well, at the medical school, the

17 undergraduate school, we teach when we're younger,

18 about age 65 we stop doing it. But I taught the

19 introductory course to neuropathology there, and

20 normal and adnormal brain development.

21 Q Doctor, are you Board Certified in any area?

22 A No.

23 Q Why don't you have any Board certifications?

24 A It was never required in the academic

25 promotions.

1 Q So because your work was focused in the
2 academic arena you weren't required to get a Board
3 certification?
4 A Right, I didn't need that credential.
5 Q Doctor, how many publications do you have?
6 A I think we counted them up. I think it was
7 about 170.
8 Q And out of those publications, do you know
9 how many relate specifically to autism?
10 A I would guess about 30.
11 Q Doctor, are you a reviewer for any journals?
12 A Multiple journals.
13 Q Can you name a few?
14 A The New England Journal of Medicine,
15 Science, Journal of Neuropathology, Experimental
16 Neurology, Journal of Compared Neurology, Neurology,
17 Annals of Neurology, Optineurapathologica. I review
18 for all of these journals.
19 Q Can you estimate approximately how many
20 articles you might have reviewed say in the past year?
21 A I get very few now because I focus my
22 interest so much, but it's just a small number in the
23 last couple of years.
24 Q But over the course of your career would you
25 say hundreds?

1 A I would guess so. I never kept track of
2 them.
3 Q Doctor, obviously your testimony today is
4 going to be focused on neuropathology. I was
5 wondering if we could start out by you telling us what
6 is neuropathology.
7 A It's the study of the diseased brain.
8 Nerves and muscle. We cover all those areas.
9 Q Where do neuropathologists obtain samples to
10 study?
11 A For routine neuropathological studies, it's
12 autopsies and surgical specimens. For my own work in
13 the autistic brain and other comparable studies, it's
14 brain banks.
15 Q What is a brain bank?
16 A They're established by the federal
17 government throughout the country. Their job is to
18 receive brains and process them in a uniform manner
19 and make them available to investigators.
20 The one I use is the Harvard Brain Bank at
21 the McLean Hospital in Belmont.
22 Q Do the brains in the brain banks, do those
23 typically come from organ donors?
24 A A lot of people just want to have their
25 brains examined, you know. Especially autistic

1 people. They feel so pressed to know what's going on,
2 wanting to help that they just donate them. So we get
3 a lot of brains that way.
4 Q What is the goal of neuropathology?
5 A For routine work, it's diagnosis which then
6 dictates treatment.
7 For my work in the anatomy of various
8 diseases, which I do mostly whole brain serial
9 sections, the idea is to find out what the
10 organization of the disease is in the brain, what is
11 the nature of the disease. That kind of creates in my
12 mind a gold standard for other investigators. So
13 whatever they find has to explain what is obvious from
14 the morphology.
15 Q Would it be fair to say that neuropathology
16 is relevant to both the diagnosis of a disease and
17 also its cause?
18 A For sure.
19 Q Dr. Kemper when did you begin researching
20 the brains of autistic individuals?
21 A The first brain we received was probably
22 around 1980, I would guess. Maybe a year or two
23 later. It was an extremely well documented brain.
24 The patient had been seen by everybody in Boston so
25 there was no question about the diagnosis. And at the

1 time we had the technique for doing whole brain serial
2 sections so we could look at every part of that brain
3 in comparison with controls.
4 So in the first report, the first
5 presentation was 1984. The publication was 1985.
6 Q You just referred to we. Who are you
7 referring to when you say --
8 A Dr. Margaret Bauman. We're the pair, we've
9 been the pair ever since --
10 Q She's a colleague of yours?
11 A Absolutely.
12 Q Would it be fair to say that you and Dr.
13 Bauman were pioneers in researching brains from
14 autistic individuals?
15 A At the time that we were following this
16 anatomy, no one had any idea of the anatomy. The
17 prevailing view was it was parenting, or some
18 environmental factor, many behavior of parents and
19 large guilt trips were laid on these people. It was
20 very comforting to me and to Dr. Bauman to find a
21 structure.
22 Q And remind me again, when did you publish
23 your first article or publication on the
24 neuropathology of autism?
25 A That was 1985.

1 Q What was the response to that?
2 A It was amazing, really. The interest in
3 that was strong. And it was on the front page of the
4 Boston Sunday Globe. It was actually carried around
5 the country as a report.
6 Q Would it be fair to say that you have
7 dedicated a substantial portion of your professional
8 life to investigating the neuropathogenisis of autism?
9 A Yes.
10 Q Doctor, before we start discussing your
11 opinions, I want to ask you a few questions about the
12 neuropathological studies generally.
13 First of all I was wondering if you could
14 comment on the number of subjects or the number of
15 brains that have been studied in this area?
16 A Actually relatively few. The problem has
17 been availability and people with interest in the
18 autistic brain.
19 Q Despite the relatively small number of
20 brains that have been studied, has there been a
21 consistency among the findings?
22 A It's really to me rather amazing. Even
23 reports from different labs in different brains are
24 showing consistent findings. We may not find the same
25 finding in every brain, but there is a consistency

1 across these series.

2 Q Another issue I was wondering if you could

3 comment on is the age of the brains that have been

4 studied.

5 A Autism is generally not diagnosable until

6 about two years of age and maybe even later. So it's

7 very unlikely that you'll get a brain early. The

8 earliest ones available for us for study is three

9 years of age.

10 Our own studies start about age four and

11 they go up into the 50s.

12 Q Are some of the brains from older

13 individuals because people don't typically die from

14 their autism? Is that a fair statement?

15 A They die maybe not from, but because.

16 Q What do you mean by that?

17 A Seizures. Some drownings. Some have had

18 appendicitis and were unable to tell their parents

19 about it. That kind of thing.

20 Q You mentioned there had been consistent

21 findings and even there are a relatively small number

22 of brains that have been studied. Are the findings

23 that have been reported in the literature consistent

24 across the age ranges of the brains that have been

25 looked at?

1 A That's correct.
2 Q The third issue I wanted to ask you about
3 generally was whether you or the other researchers
4 have been able to determine whether the brains that
5 have been looked at have come from individuals with
6 regressive autism as opposed to non-regressive autism?
7 A In the neuropathological studies it's only,
8 that information is only available on one study and
9 that's the Vargas study in which they had brains of
10 people with and without regression, finding no
11 differences in the morphology.
12 Q Have you seen any evidence that would lead
13 you to believe that there is a difference in
14 neuropathology between brains in non-regressive
15 autistics versus regressive autistics?
16 A No.
17 Q Doctor, I'd like to turn now to the opinions
18 that you're offering in this case. The first question
19 I have for you is based on your own research and your
20 review of the literature, are there structural changes
21 that have been reported in the brains of individuals
22 with autism that suggest problems in brain
23 development?
24 A There's plenty of them with brain
25 development problems.

1 Q Are there specific areas of the brain that
2 have been associated with neuropathological findings
3 in autism?
4 A The interesting feature shown here in this
5 diagram --
6 Q And we're looking at Slide 2.
7 A -- none of you people are anatomists, so I'm
8 giving you a little mini course in brain development
9 and brain anatomy, so this is it.
10 There are big black arrows there. See them?
11 The findings have been in the brain stem, in the
12 medulla. You'll hear from Dr. Rodier tomorrow about
13 the major problems in the cerebellum which are shown
14 here and labeled. And in the cerebral cortex which is
15 all the rest almost in this diagram.
16 Q So the whole area around the outside of the
17 brain is the cortex.
18 A Right.
19 Then in the lower diagram, which it kind of
20 pulls the brain apart a little bit, looking at the
21 miseal surface of the brain is the limbic system.
22 That involves a cingulate gyrus which is that first
23 area on my left, the hippocampus, amygdala, and
24 several other structures. Limbic means the limit.
25 It's the limit of the hemisphere.

1 Q We're going to get to some of the changes
2 that have been reported in some of these different
3 areas later, is that correct?
4 A Yes.
5 Q Are the findings that have been reported in
6 the literature generally, are they found universally
7 in every brain that is studied? We're now looking at
8 Slide 3.
9 A No.
10 Q Can you kind of walk us through this slide
11 and explain what some of the findings have been and
12 the relevance in terms of the consistency of those
13 findings.
14 A I know this is a busy slide. And the main
15 point that I want to make from this slide is that
16 there's a lot of pathology in almost all of the
17 brains, and there are consistent areas which seem to
18 be involved.
19 If you look at the upper panel, those are
20 eight brains from autistic individuals, from Hutsler's
21 study. Someone asked about age ranges, I can give
22 that to you. These were ages 10 to 45.
23 Q And the brains are actually represented by
24 the numbers across the top line.
25 A It says brain number. And then there's a

1 number. That's their number for each one of those
2 brains. This is the pathological changes in that
3 column that involved the cerebral cortex. Only the
4 cerebral cortex was studied in this study. Only three
5 areas, and individual blocks in those three areas. So
6 it was a very small sample but still there are quite a
7 bit of findings here.
8 The various things which are listed here,
9 I'll show you examples of and I'll go over the
10 embryology. So I'm not going to go through them now
11 except to point out that Bailey, below, the next one,
12 snows us very similar pathological changes to that
13 study of Hutsler. And Bailey in addition shows a
14 study of the brain stem and the cerebellum. He found
15 abnormalities in the normal migration in four of his
16 six brains, and he found a decreased number of
17 Purkinje cells in five of the six brains. And a
18 decreased number of Purkinje cells is the most
19 consistent report on neuropathology in the autistic
20 brain.
21 Q So based on this slide, it looks like there
22 is, even though not every change is found in every
23 brain, there are consistent findings among the brains
24 of autistic --
25 A That's right.

1 Q Dr. Kemper, what is the significance of the
2 various findings that are noted on this slide in terms
3 of brain development?
4 A This next slide here which conveniently just
5 came up --
6 Q Slide 4.
7 A -- Slide 4 is a timeline of developmental
8 events in the human brain.
9 The first one at four weeks is what Dr.
10 Rodier will be talking about is a major malformation
11 in the medulla and I'll let her explain that because
12 she's intimately involved with it.
13 The next one, it says number of mini columns
14 determined. you'll hear from Dr. Casanova. That
15 refers to his studies. Those minicolumns were
16 determined as a number very early in gestation, before
17 migration from the cortex. And that you can see is
18 way up there. That's probably around six weeks, maybe
19 even earlier, five weeks according to Pasko Rakic.
20 The next line up there is migration of the
21 neurons to the cerebral cortex. The neurons in the
22 cerebral cortex are made in one area of the brain,
23 I'll show this to you. They migrate to another area
24 of the brain, and then they settle in. It has a
25 timetable. I've indicated it here. it's roughly

1 eight weeks to anywhere from 16 to 20 weeks, all the
2 first half of gestation. I will show you examples of
3 that.
4 And I will show you examples of a similar
5 migratory stream in the brain stem from the rhombic
6 lip, gives rise to several of the neuronal structures
7 in the brain stem which are related to the cerebellum
8 and parts of the cerebellum itself.
9 You can see it is very similar in this
10 timetable to the migration to the cortical plate, but
11 ends a little earlier.
12 Then in the 1970s a whole new concept of
13 brain development arose, and I'm going to show you
14 that too. A transient population of neurons which are
15 involved in cerebral cortical circuitry early on, and
16 then later on when the cerebral cortex becomes more
17 mature, the circuits move into there. It's a holding
18 zone. It's a very impressive zone in the human brain.
19 It's larger than any animal has in a study, and it
20 extends very early in gestation to just after birth.
21 Then the next --
22 SPECIAL MASTER VOWELL: -- Is that the
23 subplate neurons that you're referring to there?
24 THE WITNESS: Yes, that's right.
25 Then the next line having to do with the

1 climbing fibers, we're able to time the defect in the
2 cerebellum by its connectivity, and its connectivity
3 are these climbing fibers, and this is a period of
4 their development. It's toward the end of gestation,
5 and we see it there.
6 The final thing I'll talk about is the
7 abnormal brain growth. The brain just comes out of
8 the womb with a shot, with a remarkably accelerated
9 growth.
10 BY MR. JOHNSON:
11 Q Now that we've kind of got an overview,
12 let's talk about some of the findings that you
13 reference on the slides. Let's now look at Slide 5.
14 Dr. Kemper, if you could first tell us what
15 part of the brain we are looking at.
16 A This is the back part. This is the medulla.
17 This is the bottom part of the brain stem. This is a
18 picture, a drawing of a human embryo. In that drawing
19 on the right there's a very large black arrow. That
20 points to a germinal zone called a rhombic lip.
21 Q What is a germinal zone?
22 A It's a zone that makes neurons. And you can
23 time developmental abnormalities from neurons derived
24 from this zone because they are born in one spot, they
25 migrate to another, and they settle in. So you can

1 know when these processes occur. If it's arrested in
2 any way then you have a good shot at the timing of
3 that malformation. The roots of migration are shown
4 in the small arrows.
5 The one on the right are little arrows just
6 beneath that black, and on the left there are a lot of
7 bent arrows. Can you see those?
8 So those are the roots of migration for
9 those neurons from the rhombic lip.
10 Derived from the rhombic lip, and I'll show
11 you examples here now, are abnormalities in inferior
12 olive and the arcuate nucleus.
13 Q Just to be clear, the neurons migrate from
14 the rhombic lip to the inferior olive?
15 A Yes.
16 Q And to the arcuate nucleus?
17 A Among others.
18 Q So the slide that we're looking at shows the
19 normal migration patterns of neurons from the rhombic
20 lip.
21 A That's correct.
22 Q Now let's look at slide six.
23 A This is one of our own personal cases here,
24 from our own collection. See where those black arrows
25 are in there?

1 Q We're looking kind of at the upper right
2 hand corner of the picture?
3 A Right. Ignore the other arrow. I'm not
4 sure what it's pointing to. But those black arrows
5 there are pointing to neurons arrested in the rhombic
6 lip germinal zone. They were arrested in their zone
7 of development.
8 Q How can we tell there's been an arrest in
9 migration from the slide?
10 A You can't. I can. I can look at it under
11 the microscope and see if they're neurons.
12 Q As you stated, this is a brain that you
13 actually personally have studied.
14 A That's right. And the Bailey paper which
15 was the second set of papers that I mentioned, had
16 neurons arrested along here, but there are no good
17 illustrations of it, so I couldn't show that.
18 Q Now let's look at Slide 7.
19 A Slide 7 on the left, there's a big black
20 arrow. Do you see it on the bottom there? And above
21 it you see a myelin stain. Above it you can see kind
22 of a sickle shaped clear area. Those are neurons,
23 and those are neurons of the arcuate nucleus in an
24 autistic brain. This is an illustration from Bailey's
25 paper.

1 Normally if you look at that brain stem on
2 the right you can see just little splotches of white
3 on the bottom. That's the normal appearance.
4 So this is an abnormally large accumulation
5 of neurons that have migrated from the rhombic lip.
6 Q Doctor, looking at this it appears that the
7 autistic brain and the normal brain are different
8 shapes. Can you explain why that's the case?
9 A Yes. The zone that I wanted to speak about,
10 the bottom, is a comparable level. The level of cut,
11 the angle of cut is slightly different on those two
12 brains.
13 Just for your orientation, the heavily
14 folded structure above there is the inferior olive
15 that we'll talk about later.
16 Q So even though they're different shapes
17 we're still looking at the same area of the brain on
18 these slides?
19 A Yes.
20 Q Now let's look at Slide 8.
21 A I'll show you this slide again for a
22 different reason. The reason we have here is that
23 this is the inferior olive. You can see that it's
24 loaded with neurons. That will be a point I'll show
25 you later on autism and control. On D on the bottom,

1 you can see that the neurons, right above the arrow,
2 are all lined up in a row. that's an abnormality.
3 That is not found in normal development. At F in the
4 bottom on the right you can see the normal appearance
5 of that region.
6 Q And just to be clear, when we're looking at
7 this there are three boxes on either side. The top
8 left hand box is labeled A and it has a small letter D
9 with a small arrow. That area is blown up in the
10 bottom picture on the left hand side.
11 A Yes.
12 That we have found in all the brains that we
13 have examined. We have our own ongoing study on
14 serial sectors of the brain stem and all of those have
15 shown that. So it's a fairly consistent abnormality.
16 And it indicates an abnormal settling in of neurons
17 into the rhombic lip, neurons that have migrated from
18 the rhombic lip.
19 Q The slides that we've just looked at, Slides
20 6, 7 and 8 that deal with the migration from the
21 neurons migrating from the rhombic lip to the inferior
22 olive, can you correlate those findings to a specific
23 period of brain development?
24 A Yes. These are probably up to about 14, 16
25 weeks of gestation. The rhombic lip is pretty close

1 in this time of origin to the migration to the
2 cerebral cortex.
3 Q Now let's look at Slide 9. What area of the
4 brain are we looking at here?
5 A This is cerebellum. This illustration is
6 from our original case but we have other examples of
7 it. What we're showing here is a loss of Purkinje
8 cells, and where Purkinje cells are severely depleted,
9 a loss of granule cells.
10 Q Could you tell us what are Purkinje cells?
11 A That's the projection cell of the cerebellar
12 cortex. It's the boss cell of the cerebellar cortex.
13 Q Are Purkinje cells the same thing as
14 pyramidal cells?
15 A No. These are GABAergic neurons. Those are
16 not.
17 Q On page 18 of Dr. Kinsbourne's report which
18 is Exhibit 30 in the William Mead case and Exhibit 26
19 in the Jordan King case, he states, "Pyramidal cells
20 are particularly vulnerable targets for excitotoxic
21 damage due to glutamate. The depletion in the number
22 of Purkinje cells in the cerebellum and frontal cortex
23 that has been demonstrated in the brains of
24 individuals with autism may in some cases represent
25 the cytotoxic effect."

1 Does that statement indicate that Dr.
2 Kinsbourne is comparing pyramidal cells to Purkinje
3 cells?
4 A It's very difficult to compare them.
5 Q They're not the same thing.
6 A They're very different.
7 Q Let's get back to Slide 9, if you can tell
8 us what this slide shows.
9 A If you look at the right hand panel, the one
10 that says from Bailey et al, you'll see two black
11 arrows. Those are pointing to Purkinje cells. This
12 is an illustration from Bailey. You can see that
13 there's no more Purkinje cells shown there.
14 Q And you would expect the Purkinje cells to
15 be where?
16 A One continuous line right along between that
17 more open zone and the zone which is density stained.
18 That's the Purkinje cell layer. And you would expect
19 space as the ones between those two arrows all the way
20 down. So this shows mild loss of Purkinje cells with
21 relative preservation of granule cells.
22 On the left hand panel the loss of Purkinje
23 cells in those areas was profound. At C you probably
24 cannot see it well, but the Purkinje cells there are
25 preserved, it's taken from an area of the cerebellum

1 which is the unaffected.

2 Q So the box labeled C is the unaffected area

3 where there are Purkinje cells are preserved.

4 A Yes. The box labeled B is a profound loss

5 of Purkinje cells. There are none in that

6 illustration. You can see there's an attendant loss

7 also of granule cells.

8 Q How can you tell there's a loss of granule

9 cells?

10 A You can compare their density. It's a very

11 dark staining layer in C, as opposed to a lighter

12 staining layer in B. You can see it.

13 Q So the dark area in box C, those are the

14 granules.

15 A Those are the granules.

16 Q And box B, the fact that it's lighter is

17 evidence that there's been a loss of granule cells.

18 A That's right. And it's well known from the

19 developmental literature that when Purkinje cells are

20 lost early in development its comparable cohort of

21 granule cells also decreases.

22 The other point I want to make in this slide

23 is that in the autistic brains, the cerebellar

24 pathology is in a more lateral part of the cerebellum.

25 Q We're now looking at box A now on the left

1 hand side?

2 A Box A. The more lateral part of the

3 cerebellum. We can see where the staining is lighter

4 than in any other spot. It extends throughout the

5 extent of the cerebellar cortex in the involved areas.

6 It shows no predilection for one place or another.

7 In the middle of the cerebellum which is

8 just almost to the far right of the illustration,

9 that's the vermis, that's the mid line of the

10 cerebellum, and it is spared in autistic brains in

11 terms of cell population loss. So there's a very

12 distinct difference between the emphasis of the

13 lateral lobe of the cerebellum and the vermis. I make

14 that point as it becomes important later on.

15 Q I believe you said earlier that the finding

16 with respect to the Purkinje cells is the most common

17 reported finding in autistic brains?

18 A Yes.

19 Q Can you date a decrease in the number of

20 Purkinje cells to a specific period of brain

21 development?

22 A We think we can.

23 Q How do you think you can do that?

24 A With this next slide.

25 Q This is Slide 10.

1 A Okay. Now I showed you that nucleus in the
2 brain stem called the inferior olive. The inferior
3 olive projects to the cerebellum. To the Purkinje
4 cells. That projection is that one inferior olivary
5 neuron only projects about 15 Purkinje cells, so it's
6 a very tight projection. As you can see in the middle
7 diagram labeled climbing fiber, you can see a little
8 worm-like thing going up to the Purkinje cell. Then
9 that axon completely engulfing the cell body and
10 dendritic tree of the Purkinje cell.
11 Q The Purkinje cell in that illustration is
12 the entire body that's shown there.
13 A That's right.
14 SPECIAL MASTER VOWELL: You lost me. Start
15 with that again.
16 We're looking at the center box where it
17 says climbing fiber?
18 THE WITNESS: That's correct.
19 SPECIAL MASTER VOWELL: Where on there is
20 the climbing fiber?
21 THE WITNESS: All those black lines along
22 the Purkinje cell are climbing fibers.
23 SPECIAL MASTER VOWELL: So all the black
24 lines from C all the way to the top of the diagram are
25 climbing fibers.

1 THE WITNESS: That's right. That is the
2 dendritic tree. You can see it just from the climbing
3 fibers.
4 SPECIAL MASTER VOWELL: So the climbing
5 fibers create the dendritic tree?
6 THE WITNESS: No, they surround it. It's
7 part of the facilitatory synaptic relationships of the
8 brain stem to the Purkinje cell. Okay?
9 That climbing fiber that I showed you there
10 reaches the Purkinje cell at about 29-30 weeks of
11 gestation. Prior to that time it is not involved with
12 the Purkinje cell. And since we know that the loss of
13 Purkinje cells from birth on out lead to loss of
14 inferior olivary neurons, we're very impressed with
15 this autistic brain in there was no loss of the
16 olivary neurons.
17 So the normal connectivity between these
18 climbing fibers and the Purkinje cells we assume was
19 not in place at that time.
20 BY MR. JOHNSON:
21 Q Just to make sure that I'm clear, the
22 climbing fiber reaches the Purkinje cell around 29 or
23 30 weeks of gestation, is that right?
24 A That's right.
25 Q And normal brains, if Purkinje cells are

1 lost after they've already been formed then the
2 inferior olivary neuron goes away as well.
3 A That's right.
4 Q And in autistic brains the Purkinje cells
5 are not there but the inferior olivary neurons are
6 still there.
7 A Yes, that's correct.
8 Q From that you conclude that the Purkinje
9 cells were gone before the relationship between the
10 climbing fiber and the Purkinje cell was established.
11 A Yes, that's our best guess on that.
12 Q And just to clear up, on the left side of
13 the slide, the red lines represent what?
14 A On that slide the red blobs are the Purkinje
15 cells and the dendrites are red. And the blue is the
16 climbing fiber climbing up the Purkinje cell.
17 Q So this is just another representation of
18 the development of the relationship between the
19 climbing fiber and the Purkinje cell.
20 A Yes. That's right.
21 Q Again, this slide shows what happens during
22 normal development, normal brain development.
23 A Yes.
24 Q Let's look at Slide 11. What does this
25 slide show?

1 A This one I'll have to walk you through a
2 bit. It's not intuitively obvious looking at it
3 what's going on. This is an illustration that was
4 made by Pasko Rakic in '82.
5 On the left is a diagram of what the
6 cerebellar cortex looks like at nine weeks of
7 gestation.
8 None of the layers are visible.
9 The next one is 13. The next one is 16, 21,
10 25, 30, 40, and seven postnatal months. So that's
11 where they are. That's what they look like.
12 I want to call your attention to the one
13 where the dark arrows are. That is 25 weeks of
14 gestation in the human brain.
15 The left hand arrow points to an area where
16 there's a clear area there. Can you see it? There's
17 a clear area there and that's called a laminam
18 desicans in our terminology.
19 What they find out when they look at what's
20 in that clear area at that time, it is the climbing
21 fibers. They are there, but they have not yet
22 innervated the Purkinje cells. It's a holding zone
23 for circuitry.
24 In the next five weeks they envelop the
25 Purkinje cell. And by the time of birth they envelope

1 it as densely as I showed you in the previous
2 illustration.
3 Q So in Slide 11 at 30 weeks, that is showing
4 the climbing fibers have reached and enervated the
5 Purkinje cells.
6 A Yes, have left their holding zone.
7 Q Is it this study that you're using as the
8 basis for determining that the climbing fibers
9 established the relationship with the Purkinje cells
10 between 29 and 30 weeks of gestation.
11 A Right. Also there's a very comparable study
12 by Marintha Dia, a Golgi study which shows essentially
13 the same thing.
14 Q Now let's look at Slide 12.
15 A In the report that I gave you I talk about
16 large neurons so I want to show you an example of
17 large neurons.
18 Q Again, what area of the brain are we looking
19 at here?
20 A This is the inferior olive.
21 In childhood in our own brains, we have
22 several brains up to about 13 years of age. Up to
23 that time we see this pattern. You can see in the
24 panel at the top, Panel A, an arrow.
25 Below it you can see Panel C. You can see

1 how large those neurons are in the autistic brain.
2 And on the right hand side at E is that exact region
3 in an age and sex-matched control. You can see this
4 unusual pattern of cell size.
5 Q Let's look at Slide 13.
6 A In the older brains, and these are brains
7 over 17 years of age. There's a gap in our material
8 there between 13 and 17, so we don't know what happens
9 there. You can see that the cells now are small.
10 Q Slides 12 and 13, what do those changes
11 signify for you?
12 A It's been a difficult one to interpret,
13 because enlargement of neurons of this type is a very
14 unusual neuropathology. There's very little
15 literature on it. The vast majority of the literature
16 has to do with the inferior olive. The inferior olive
17 receives as a projection from the red nucleus via the
18 central tegmental tract a massive projection. Lesions
19 in that central tegmental tract lead to these
20 abnormally large neurons. So it's a disturbance of
21 connectivity.
22 Other illustrations in the literature of
23 enlarged neurons also call attention to the fact that
24 there is disturbed connectivity. So to me this means
25 that the circuitry in the cerebellum is not normal.

1 Q Again, these slides are more examples of
2 disturbances in development.
3 A And connectivity.
4 Q Dr. Kemper, at what point in development do
5 the changes that we just looked at relate to?
6 A These extend from childhood up into adults.
7 Q Now let's look at Slide 14.
8 A This is your next lesson in brain
9 development.
10 Q We're now moving on and talking about --
11 A This is the cerebral cortex. This is the
12 development of the cerebral cortex.
13 In 1970 a whole new concept had appeared in
14 the development of the cerebral cortex. I want to go
15 over that with you because it will become important
16 for you to understand when you see the slides that I
17 will show. This was described well by rin bedea (ph).
18 On that lower panel where I've colored it in
19 yellow to make it easier for you to see is a zone
20 called the primordial plexiform layer. You can see in
21 the next panel it gets larger. And you can see in the
22 next panel, the second from the last, that it's
23 suddenly split into two zones.
24 Q And it has Bd beneath it, is that correct?
25 A The bottom zone is the subplate that I

1 mentioned.
2 Q The bottom yellow zone.
3 A The bottom yellow zone is subplate, and the
4 top yellow zone is layer one of the cerebral cortex.
5 And in between are the definitive neurons of the
6 definitive cerebral cortex.
7 So the neurons which make the cerebral
8 cortex were born between these two zones.
9 The reason that's important is that that
10 zone which I've labeled subplate here, persists in the
11 human brain up until just shortly after birth and
12 disappears.
13 Experimental studies show it's very
14 important for the establishment of cerebral cortical
15 circuitry.
16 Q What is in layer one?
17 A Layer one is just the top layer of the
18 cerebral cortex.
19 Q Are there many neurons in layer one?
20 A At this stage there are a lot. But in the
21 adult brain they're very infrequent.
22 Q Let's move on now and look at Slide 15.
23 A This is to show there are no good examples
24 in the neuropathology literature of neurons arrested
25 at the germinal zone for the cerebral cortex, and

1 there are no good examples of neurons arrested in the
2 migration.
3 The examples that are available for us in
4 the autistic brain are examples of abnormal settling
5 of neurons or abnormal disposition of neurons within
6 the cerebral cortex.
7 Q And this is referring to the process of
8 development we were just looking at on the last slide,
9 correct?
10 A That's right.
11 On the left is the most profound
12 malformation outside of the one that Dr. Rodier will
13 show you. This is the most profound that we have
14 found.
15 This is an abnormally folded cortex. There
16 are about three or four times as many folds as one
17 would anticipate normally. So this is called a
18 polymicrogyria, too many small gyri.
19 Q And are you referring to the kind of
20 fingerlike projections into the dark area?
21 A That's right.
22 The pathogenesis of this has been well
23 worked out. It involves some kind of a destructive
24 process in the cerebral cortex around the end of
25 migration, and then the migration of neurons into this

1 area.

2 The next one labeled Bailey et al shows

3 disoriented pyramids in the cerebral cortex. If you

4 look at those cells in there -- This would be like a

5 more normally oriented cell. The apical dendrite that

6 process in the top is just heading straight up.

7 Q You're pointing to the darker kind of

8 pyramid-shaped area?

9 A That's right.

10 This one here is tipped, this one here is

11 tilted, this one here is abnormal. So there's marked

12 abnormalities in the orientation of these neurons. So

13 presumably something is wrong with the settling in of

14 these neurons.

15 Q Again, how are they normally oriented?

16 A Straight up, this way.

17 See, this one's oriented this way; this

18 one's oriented this way; this one's oriented this way.

19 Those all should go straight up.

20 Q The third picture labeled C, what does that

21 show?

22 A Those are misplaced neurons. Those are

23 abnormally large neurons in an area of the cortical

24 plate. You would not find those normally.

25 Q And you're referring to the boxed area with

1 the arrow in it.

2 A Yes.

3 Q Where are those neurons supposed to be?

4 A Most likely up here.

5 Q Towards the top of that picture.

6 A That's right.

7 Q Does this indicate that the neurons stopped

8 during their migration?

9 A Yes. That would be the interpretation.

10 Q Let's look at Slide 16. If you can tell us

11 what this slide shows.

12 A This was a fairly striking malformation in

13 another autistic brain. To show you they're not

14 infrequent.

15 What you have here in this autistic brain,

16 this is a cingulate gyrus, the anterior cingulate

17 gyrus. An unusually clear zone here, see it?

18 Q And you're pointing to, in the top picture,

19 the top left hand picture there's kind of a blue swirl

20 and you're pointing to the middle area of that swirl.

21 A That's right.

22 Here it is under higher magnification. You

23 can see that the cortical plate is kind of disrupted

24 in its development. There should be neurons here.

25 There are not neurons here. This would be the normal

1 appearance.
2 Q The picture on the right lower side.
3 A Yes. This is a normal control. So this
4 would abe another example of a malformation in a
5 cortical plate.
6 Q Let's move on to Slide 17.
7 A This is one I'll have to work on a little
8 bit with you.
9 In all of the autopsy series that have been
10 reported, mainly the ones of Hutsler and the one of
11 Bailey, they have reported an increased number of
12 neurons on the white matter. Those increased number
13 of neurons in the white matter are in that so-called
14 sub-plate zone that I showed you in yellow earlier on.
15 This is an example of that. In the seat of
16 the gyrus in a human brain, here is just the lower
17 layer of the cortical plate. This is white matter.
18 This is stained for cell bodies.
19 Q You're pointing to the right upper hand box
20 -- Sorry, the left upper hand box.
21 A Yes.
22 Q At the top are dark blue dots and the bottom
23 is lighter blue. Explain again the significance of
24 that.
25 A This is to show it enlarged, because the

1 neurons are not very large, that indeed these are
2 neurons there in that white matter. This is the
3 control brain showing only an occasional neuron in
4 that region.
5 The other thing that this slide illustrates,
6 which is pointed out in those autopsy series, is the
7 demarcation between the cortex and the white matter is
8 not as striking as it is normally. You can see it
9 here.
10 Q And the control, there is more of a clear
11 transition between the darker blue and the lighter
12 blue area.
13 A Yes. So this is another change that has
14 been reported in the autistic brain that you can see
15 in this particular slide here.
16 These neurons, these sub-plate neurons have
17 been noted in numerous brains, they've been noticed in
18 the schizophrenic brain as well, and that zone is, as
19 I mentioned, a gigantic synaptic zone during
20 development. And these cells should disappear shortly
21 after birth.
22 Q Now let's look at Slide 18. What does this
23 slide show?
24 A Oh, it's improved. Okay.
25 This is from Hutsler. This is the layer one

1 of the cortex. This is the surface of the brian up
2 here.
3 Q You're pointing to the top of the picture.
4 A The top of the picture. This is layer one.
5 And layer two here, which is the cellular layer. So
6 this is the cell layer of the cortex and this is the
7 layer one. There are just large numbers of neurons
8 there, maybe multiple times more than there ever
9 should be there. And this is another thing which has
10 been pointed out in our own material as well as those
11 autopsy series that I mentioned.
12 I take these two observations, these
13 increased number of neurons in layer one, and
14 increased number of neurons in the white matter in
15 what was subplate, to indicate a persistence of the
16 embryonic zone.
17 Q So Slides 15 through 18 that we just looked
18 at, those are examples that have been reported in
19 malformations during the development of the cortex?
20 A This is correct.
21 SPECIAL MASTER VOWELL: Doctor, let me
22 interrupt you just for a second.
23 Are you saying there is an increased number
24 of neurons in the brain, or that there are an
25 increased number in the wrong place?

1 THE WITNESS: Only in the white matter. Only
2 beneath the cerebral cortex.
3 SPECIAL MASTER VOWELL: So the increase is
4 just in the cerebral cortex. Here in layer one --
5 THE WITNESS: Just below it.
6 SPECIAL MASTER VOWELL: I understood that.
7 But here in layer one and layer two you're talking
8 about, are the neurons in the wrong place or are there
9 too many of them?
10 THE WITNESS: Too many. That's a good
11 point, thank you.
12 MR. JOHNSON: Thank you.
13 SPECIAL MASTER VOWELL: Sorry to interrupt,
14 but I --
15 THE WITNESS: No, no.
16 BY MR. JOHNSON:
17 Q Again, Doctor, what period of brain
18 development are the changes in the cortex associated
19 with?
20 A The first set that I showed you are
21 associated with the migration of the neurons into the
22 cortical plate. That has been studied several times
23 at the War Museum where I was when I was there. The
24 settling in of those neurons, finally settling in of
25 the neurons into the cortical plate is not sharp, but

1 it's somewhere between 16 and maybe 20 weeks,
2 somewhere in there.
3 Q Of gestation.
4 A Of gestation.
5 Q Let's look at Slide 19. What area of the
6 brain are we looking at here?
7 A This is the hippocampus. This is your
8 memory circuits. This is where you remember your
9 daily events is here. The cells, the dark band here,
10 are classically divided into CA fields, all the way
11 down into one, and I've labeled them here. And then
12 there's a subiculum. The memory circuits in here are
13 sequential from one cell group to another. It's
14 called the trisynaptic circuit. On the top is the
15 autistic brain, and on the bottom is the control
16 brain. And the first thing you can see up here is in
17 comparison to here. It looks collapsed.
18 Q And you're looking at boxes labeled A and C.
19 A A and C, and labeled CA4. And the cells
20 appear more tightly packed together.
21 Q In the autism brain.
22 A In the autistic brain, that's right.
23 And you can look here, for instance, here --
24 CA1 in the autistic brain and you can look here in the
25 control and you can see how much further apart these

1 cells appear to be spaced.

2 The way the information gets into this

3 memory circuit is through a part of the brain called

4 the entorhinal cortex, right next to this hippocampal

5 complex. They're right next to each other. You can

6 see in the autistic brain, we have a similar

7 impression that the cells are more tightly packed.

8 You can compare it here and here.

9 The next slide is a higher power view of two

10 of these CA fields. Here's the autistic brain and

11 here's the control.

12 SPECIAL MASTER VOWELL: We're on Slide 20

13 now.

14 THE WITNESS: Yes, Slide 20.

15 The cells appear pale, and to our eyes

16 slightly more tightly packed. Here they are in the

17 CA1.

18 BY MR. JOHNSON:

19 Q Can you relate these changes to a specific

20 period of brain development?

21 A No. That's one of the ones we're really

22 unable to time. The timing depends on migrations and

23 synaptic hookups and so forth, and we just don't have

24 it here.

25 Q Let's look at Slide 21.

1 A This is the distribution of that change as
2 Dr. Bauman and I saw it. This was the mesial surface
3 of the brain, just cut this way.
4 Q Down the middle.
5 A Right down the middle. It involves the
6 migdula, the hippocampus, the entorhinal cortex, the
7 septum and mammillary body. These are key components
8 of the limpic system. This is a key system involved
9 in motion.
10 Q Doctor, before we move on to the next slide,
11 we've gone through some examples of the changes that
12 have been reported in autistic brains. Would it be
13 fair to say that the literature supports the
14 conclusion that the structural changes that have been
15 observed in autistic brains most likely occur
16 prenatally?
17 A The majority of them, yes.
18 Q And I believe on Slide 2 you identified one
19 finding that related to subplate neurons that may be
20 associated with brain development that extends to just
21 after birth.
22 A That's correct.
23 Q You reviewed Dr. Kinsbourne's report, is
24 that correct?
25 A Yes.

1 Q Is Dr. Kinsbourne proposing a mechanism by
2 which Thimerosal from vaccines interferes with
3 neuronal development?
4 A No.
5 Q Is Dr. Kinsbourne proposing a mechanism that
6 involves any of the developmental processes that
7 you've discussed here today?
8 A No.
9 Q Another of Petitioner's experts, Dr.
10 Aposhian, listed six pillars that he believes support
11 the conclusion that Thimerosal-containing vaccines can
12 contribute to the development of autism, and the sixth
13 of those pillars was based on the Courchesne article
14 which is Petitioner's Master List No. 104.
15 Dr. Aposhian says that this article provides
16 evidence of post-natal loss of brain cells in the
17 cerebellum of autistic individuals.
18 Have you reviewed the Courchesne article?
19 A Yes, I have.
20 Q Do you interpret that article as saying that
21 there is post-natal loss of brain cells in the
22 cerebellum of autistic --
23 A No, I don't. If our interpretation is
24 correct and they were lost early, there's no reason
25 for them to form again. So no matter what stage of

1 development later on you look at, it would be the
2 same.
3 Q And is that article, in the part of that
4 article that deals with that, are they talking about
5 the decrease in the number of Purkinje cells?
6 A That's right.
7 Q And again, going back to the slides that you
8 presented earlier, is your opinion that there is not a
9 loss of Purkinje cells based on the notion that the
10 Purkinje cells just weren't there to begin with?
11 A It's really hard to know whether they were
12 there to begin with or not.
13 Q But in any event, they were lost before they
14 established the relationship with the climbing fibers.
15 A That's correct, yes.
16 Q Doctor, in your report you also addressed
17 the issue of abnormal post-natal brain growth. I was
18 wondering if you could just briefly summarize the
19 findings that have been reported in the literature on
20 this issue.
21 A Sure.
22 Q We're now looking at Slide 22.
23 A There are large numbers of papers on this
24 abnormal brain growth. I just selected a few here to
25 show. The one on the left, Redcay and Courchesne, was

1 a meta-analysis study. He had autopsy brain weights,
2 he had MRI measurements of brain size, he had head
3 circumference, and he adjusted these various different
4 kinds to make them more or less comparable. And put
5 them together in this diagram shown on the top here.
6 And you can see that this is zero at birth, and on the
7 far right is 36 years, so you can get an idea of the
8 span of that. You can see right after birth, it just
9 shoots up in a gigantic burst of brain growth.
10 According to Jerry Dawson's more recent paper, that
11 spurt of growth may be confined to the first year of
12 life. Then brain growth slows and finally just almost
13 comes to a standstill whereas the normal brain
14 continues to grow.
15 So by the time you're in adolescence, the
16 brain size is the same as the controls. So there's
17 this peculiar feature of it. On the lower left is
18 Courchesne's paper which is widely, the illustration
19 is widely used, and the --
20 It doesn't look like it's real clearly
21 projected here.
22 Okay.
23 The first bar is birth. And in Courchesne's
24 view of the head circumference, it may be a little bit
25 low at birth, others show that it looks normal at

1 birth. Hobbs shows that it's normal during pregnancy,
2 viewing scans.
3 You can see by three to five months in his
4 study, the brain is now enlarging.
5 By six to 14 months, he bunched the data
6 together, there was a significant increase in brain
7 size.
8 The next panel, labeled Table 3 on there.
9 Q This is the Dementieva cite?
10 A Yes, the lower right. That's from
11 Dementieva. That was a large study of head
12 circumferences. Within that study of his the head
13 measurements of children at birth and one month of
14 age, then you had children from one month to two
15 months of age, then from two to six months, and six to
16 twelve months. So they could look at the rate of
17 growth in these different age periods. Do you follow
18 me?
19 In that study there was a remarkable
20 increase in growth in the first month.
21 Q So in short, the studies are showing the
22 there is rapid and significant brain growth in the
23 first few months of life in these autistic brains?
24 A That's right.
25 There's one more point I'd like to make.

1 There's Lainhart, at the bottom. This is a particular
2 measurements. The age range was three to 47 years.
3 These are all from the collaborative studies on autism
4 funded by the National Institutes of Health. The
5 measurement of head circumference can be chancy, and
6 the autism people are so interested in this that they
7 want to be carefully specified as to how these heads
8 are measured, so they're uniformly measured.
9 In this large sample here, the distribution
10 curve of the head circumference was unimodal. There
11 wasn't a large group and another group and a small
12 group. It was a unimodal distribution curve. The
13 shape of the curve was normal, it wasn't skewed, and
14 it was shifted to the right. That shift to the right
15 suggested to them that an increase in head size
16 probably affected all of the individuals.
17 That's my statement there.
18 Q Has anyone come up with a good theory that
19 explains abnormal post-natal head growth?
20 A There are a lot of ideas, but I don't see
21 any of them that really work. One of the more popular
22 ones is one that you'll hear from Dr. Casanova I think
23 in a couple of days where he suggests there's an
24 increased number of minicolumns and that may indeed be
25 part of it.

1 I've been through the entire literature
2 looking for that very issue, and one thing that did
3 show up which intrigued me very very much is in the
4 dyslexic brain there are also focal malformations in
5 the cortical plate. They're different than the ones
6 that are here, but they certainly are there. You can
7 see these. They call them brain warts, hermwartzen.
8 And there's an experimental animal that has this.
9 It's an animal model of autoimmune disease. You can
10 see these little warts in these rats.
11 So they look at the connectivity of these
12 little warts, which are malformations. And they found
13 there's enhanced local connectivity and decreased
14 colossal connectivity. So it may be that these
15 malformations in some way are related. It could be
16 that the minicolumns in some way are related. But the
17 timing for synaptic elimination doesn't fit. I've
18 looked into that. The timing of elimination of axons
19 doesn't work because the axons we try to eliminate are
20 very thin on myelinated axons, they almost have no
21 mass to them at all. So it's really a mystery. And
22 why it's so abrupt and so sudden after birth I think
23 is an amazing thing.
24 Q In your opinion, is abnormal post-natal head
25 growth consistent with exposure to ethyl mercury from

1 Thimerosal-containing vaccines?
2 A No. Those generally make brains smaller.
3 I've looked through the literature for large brains
4 from mercury toxicity and have been unable to find an
5 example.
6 Q You just mentioned you looked at some
7 literature on mercury toxicity. Have you reviewed
8 literature that addresses the neuropathology of
9 mercury toxicity?
10 A Yes, I have.
11 Q What did you find?
12 A This.
13 Q We're now looking at Slide 23.
14 A These are summary slides.
15 The pathology is very consistent from report
16 to report as to the areas of predilection for the
17 toxicity of mercury. And this Reuhl and Chang, the
18 one on the right there, shows a person who has been
19 exposed as an adult, the next one is an infant, and
20 then an earlier stage of development showing the
21 increase of vulnerability of a more immature brain to
22 mercury toxicity. These are mainly from the Minimata
23 Bay study.
24 The area of predilection, I'll show you here
25 with the pointer, visual cortex, almost always

1 involved, visual cortex. And it involves more
2 peripheral parts of the visual field initially. So a
3 common complaint of people with mercury toxicity is
4 tunnel vision, then eventually blindness. This area
5 up here, this is the motor cortex, this is the sensory
6 cortex. So this is another area of predilection.
7 In this diagram on the left, the only reason
8 I include it, is the superior temple gyrus. It's the
9 auditory cortex. Deafness has been reported.
10 Another area I want to call your attention
11 to is the cerebellum. Almost universally involved
12 with mercury toxicity. There are destructive lesions.
13 Neurons are killed by mercury toxicity in the motor
14 sensory cortex, the visual cortex, auditory cortex and
15 cerebellum. So it's a very destructive process.
16 Q Now let's look at Slide 24.
17 A The reason I spent so much time on that
18 cerebellar slide in the autism is for contrast now
19 with this slide. All of the literature in the
20 cerebellar involvement points out this anomoly. It
21 involves the deeper parts of the cerebellum.
22 Q You're pointing to the lower right hand
23 portion of the top left hand picture.
24 A Yes, thank you. And here is the preserve
25 area.

1 Q Those are darker areas on the edges.
2 A That's right.
3 And this one is Greenfield, which is our
4 standard neuropathology text. A very mild
5 involvement. You can see the exact same thing. Deep,
6 not on the surface of the cerebellum.
7 The other point to be made is this is the
8 vermis, this is the mid-line of the cerebellum. That
9 is the area of predilection. The area of predilection
10 in the autistic brains is not there, it's the lateral
11 lobe. The autistic individual, the loss of Purkinje
12 and granule cells extends all the way to the surface
13 of the cerebellum.
14 The other feature which has been brought up
15 in all the papers, see these black dots here.
16 Q You're pointing to the area in the top right
17 hand picture where it says Purkinje cell layer.
18 A Yes, Purkinje cell layer and granule cell
19 layer. Even down here, it's even easier to see. All
20 these dark torpedo-looking things, these are Purkinje
21 cells. And there are virtually no granule cells. So
22 the predilection, there's a striking predilection for
23 the granule cells with, for the most part preservation
24 of Purkinje cells. It's a striking difference from
25 the autistic brain which is just the reverse of this.

1 Q Let's look at Slide 25.
2 A This is from Shiraki. On the left here,
3 myelin stain. Myelin stain you can really see the
4 brain the best for our illustration. Where the big
5 arrow is here, this is the position of the visual
6 cortex. This is where the visual cortex is. It
7 should look like this, but it doesn't. It's severely
8 destroyed.
9 Q So it should be darker.
10 A Right, it should look like this, and it's
11 just the myelin's gone, the cortical plate is gone,
12 and if you look at this, which is a lovely adjacent
13 section to that one. It's stained for elemental
14 mercury. That plus means it's stained for, it should
15 have two X's. You can see the deposition of the
16 mercury very closely mirrors the destruction of the
17 brain.
18 In this brain here you can see it also.
19 This is the auditory cortex. Also severely involved.
20 Q So based on your review of the literature
21 and your knowledge of the neuropathology of autism and
22 mercury toxicity, do you have an opinion as to whether
23 they are consistent?
24 A No.
25 Q You do not have an opinion or --

1 A No, I don't think they're consistent.
2 (Laughter).
3 Q Can you summarize the differences between
4 the neuropathology of mercury toxicity versus the
5 neuropathology of autism? This is Slide 26.
6 A I've shown you or discussed most of this
7 already. Karen Nelson and Margaret Bauman have also
8 reviewed this as well in the literature.
9 On the left is what's found in the autistic
10 brain, on the right is what's found in the brain with
11 mercury toxicity.
12 The initial clinical feature of mercury
13 toxicity is a sensory neuropathy. They have numbness
14 and tingling in their feet. This is not a clinical
15 feature of autism. Restrictions of visual field is a
16 classic finding in mercury toxicity, is not found in
17 autism. Ataxia and dysarthria is our description as
18 neurologists for the deficits from the cerebellar
19 lesion. It is a prominent deficit in mercury toxicity
20 and there's no trace of it in the clinical picture of
21 autism.
22 Neuropathology. I showed you abnormal brain
23 growth. There's no evidence of an abnormal increase
24 in brain size in the mercury toxicity and many of the
25 reports report small brains. Autism, no evidence of

1 involvement of peripheral nerve in autopsy.
2 Involvement on peripheral nerve noted on many
3 autopsies, the illustrations didn't lend themselves
4 well for this. I didn't show them to you.
5 Involvement of the hippocampus; spared in
6 lead (sic) toxicity. Cerebellar loss of Purkinje
7 cells. I'm sorry. Cerebellum with loss of Purkinje
8 cells; preservation of Purkinje cells. Secondary loss
9 of granule cells; primary involvement of granule
10 cells. Predilection for lateral lobes in autism;
11 midline in mercury toxicity. Predilection for deep
12 folia in mercury toxicity; no predilection for deep
13 folia in autism. Marked neuronal loss in cortex, and
14 I showed you also myelin; no neuronal loss in cerebral
15 cortex. Marked predilection for visual cortex; no
16 predilection for visual cortex. We surveyed it in all
17 of our brains and we never found an abnormality.
18 Q So in summary, would it be fair to say there
19 are numerous marked differences between mercury
20 toxicity and autism?
21 A No overlap.
22 MR. JOHNSON: Special Master, I have a
23 little while longer, and this is kind of a natural
24 breaking point. I don't know if it would be
25 appropriate to break for lunch at this point.

1 SPECIAL MASTER VOWELL: It's about 1:00
2 o'clock. This may be a good time to break.
3 You're going to want a break, I understand,
4 before you begin your cross-examination, but we can
5 give you some time to get started on it, Mr. Powers.
6 MR. POWERS: Thank you very much.
7 SPECIAL MASTER VOWELL: Let's go ahead and
8 take a break. An hour lunch, so if we could reconvene
9 at 2:05.
10 (Whereupon, at 1:05 p.m. a luncheon recess
11 was taken, to reconvene at 2:05 p.m. this same day,
12 Thursday, May 22, 2008.)
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1 A F T E R N O O N S E S S I O N
2 (2:05 p.m.)
3 SPECIAL MASTER VOWELL: We're back on the
4 record. Mr. Johnson, you may complete your direct
5 exam.
6 MR. JOHNSON: Thank you, Special Master.
7 DIRECT EXAMINATION (Cont'd)
8 BY MR. JOHNSON:
9 Q Dr. Kemper, before lunch you were discussing
10 the neuropathology of mercury toxicity as compared to
11 the neuropathology of autism.
12 A Yes.
13 Q Petitioners have presented a hypothesis in
14 this case that rather than a direct toxic effect it is
15 persistent inorganic mercury in the brain causing
16 inflammation that leads to autism. They've relied
17 primarily on work by Vargas to support this
18 hypothesis.
19 Have you reviewed the work of Drs. Vargas,
20 Zimmerman and Pardo?
21 A Yes.
22 Q And just for the record, Vargas is
23 Petitioner's Master List 69; there is a Pardo article
24 at Petitioner's Master List 72; and a Zimmerman
25 article at Petitioner's Master List 555.

1 Dr. Kemper, do you personally know Drs.
2 Zimmerman and Pardo?
3 A Yes, I do. Particularly Dr. Zimmerman.
4 Q Have you discussed their work with them?
5 A Yes, I have.
6 Q In fact during one of the meetings that we
7 had with you did you inform us that you had spoken to
8 Dr. Pardo about his work?
9 A Yes, I did.
10 Q Can you describe that conversation?
11 A Well, I met him at a meeting that we had,
12 convened for autism. He had given a paper there, on
13 his work on the immune system. I was particularly
14 interested to hear his views from himself, what he
15 thought the relationship between his innate immune
16 response, neuro immune response was to the
17 pathological changes we had seen in the autistic
18 brain.
19 Q During that meeting did you recommend that
20 we speak to Dr. Pardo?
21 A Yes.
22 Q Did you recently receive a letter from Dr.
23 Pardo?
24 A Yes.
25 Q Are the statements contained in Dr. Pardo's

1 letter consistent with the discussion that you had
2 with him?
3 A Yes.
4 Q Dr. Kemper, what is microglial activation?
5 A That means that the glial cells are more
6 prominent within the tissue in general. The nucleus
7 may be larger. Particularly the cytoplasm and the
8 prozisis (ph) are enlarged.
9 Q On page 13 of his report, we're pulling it
10 up for you now. Actually, maybe not.
11 On page 13 of his report Dr. Kinsbourne
12 lists the characteristics of neuro inflammation as
13 follows. He says it involves edema, activation of
14 microglia and local invasion of immune cells from the
15 circulation.
16 Would you agree that this is an accurate
17 description of neuro inflammation?
18 A Only the glial cell response.
19 Q Did Dr. Pardo and his colleagues indicate
20 anywhere in their publications that edema is present
21 in neuro inflammation?
22 A No, and we've found no evidence of it
23 either.
24 Q And did Dr. Pardo and his colleagues
25 indicate that local invasion of immune cells from the

1 circulation occurs in neuro inflammation?
2 A No.
3 Q In fact would that be consistent with Dr.
4 Pardo's findings?
5 A Yes, he reported the lack of an adaptive
6 immune response with the glial cells.
7 Q So the local invasion of immune cells refers
8 to an adaptive immune response?
9 A That's correct.
10 Q Do you believe that Dr. Kinsbourne's
11 description of neuro inflammation is incorrect?
12 A Yes.
13 Q Dr. Kemper, is microglial activation present
14 during normal brain development?
15 A Yes, it is.
16 Q So just to be clear, microglial activation,
17 it's not specific to the presence of a neuro toxin
18 such as mercury?
19 A That is correct.
20 Q Does Dr. Pardo say whether it is possible
21 that developmental abnormalities present since
22 gestation could produce microglial activation?
23 A Yes, he did.
24 Q Does Dr. Pardo state that prenatal neuro
25 developmental abnormalities are consistent with neuro

1 inflammation?

2 A Yes.

3 Q To your knowledge does the Vargas paper also

4 mention the possibility that activated microglia

5 reflects continued patterns of abnormal development

6 that began prenatally?

7 A Certainly.

8 Q Doctor, to your knowledge can microglial

9 activation be a beneficial process?

10 A Yes.

11 Q And did the Vargas paper discuss any place

12 the idea that microglial activation can act as a neuro

13 protectant?

14 A Yes, it was a major point.

15 Q To your knowledge, could microglial

16 activation be a response to a disease rather than its

17 cause?

18 A Yes.

19 Q Based on your review of Dr. Pardo's work and

20 his letter, does he assume that microglial activation

21 is causing autistic symptoms?

22 A No.

23 Q I want to talk now a little bit about

24 astrocytes. On page 17 of his report Dr. Kinsbourne

25 states that activated microglia could kill astrocytes

1 with friendly fire. Does that statement suggest to
2 you that part of Dr. Kinsbourne's hypothesis is that
3 astrocytes are dying?
4 A Yes.
5 Q And on page 13 of his report Dr. Kinsbourne
6 called gliosis the sequel of the death of astrocytes
7 in inflammation. Is that a correct description of
8 gliosis?
9 A No.
10 Q What is gliosis?
11 A Gliosis is enlargement of the glial cell
12 body nucleus as well as the cytoplasm, more prominent
13 for processes and more readily stained with the glial
14 fibrial acidic protein.
15 Q Do you see astrocyte death with gliosis?
16 A No.
17 Q When Dr. Kinsbourne on page 13 of his report
18 says that gliosis, the presence of gliosis in autistic
19 individuals provides dramatic support for his
20 hypothesis, do you agree with that?
21 A No.
22 Q Based on your review of the Vargas work, did
23 they see increased or decreased astrocyte activation
24 in autistic brains?
25 A Increased.

1 Q Is this finding consistent with Dr.
2 Kinsbourne's hypothesis of astrocyte death?
3 A No. There was no death reported there.
4 Q Based on the work of Vargas and Dr. Pardo
5 and Dr. Pardo's letter, in your opinion is astrocyte
6 activation consistent with Dr. Kinsbourne's suggestion
7 of astrocyte death?
8 A No.
9 Q When he testified Dr. Kinsbourne stated that
10 astrocyte death may not be necessary to his model, but
11 maybe a malfunction or inactivation of astrocytes
12 would be enough.
13 Is increased astrocyte activation as shown
14 in the Vargas study consistent with malfunction of
15 astrocytes that Dr. Kinsbourne testified about?
16 A Not that I know of.
17 Q Would you say, based on your review of the
18 Vargas work, that their findings are inconsistent with
19 our Kinsbourne statement that astrocytes are dead or
20 no longer active in autistic brains?
21 A Yes.
22 Q Doctor, did the authors of the Vargas paper
23 try to correlate neuro inflammation to regressive
24 autism?
25 A No. As a matter of fact they made a point

1 that several of their patients had regressive autism
2 and there's no difference in the immune response
3 between those that did and those that did not.
4 Q So just to be clear, they did look for a
5 correlation.
6 A They did.
7 Q And they found neuro-inflammation in both
8 the regressive and non-regressive --
9 A That's right. No correlation.
10 Q Did Drs. Pardo, Zimmerman or Vargas conclude
11 anywhere in their articles that neuro inflammation is
12 the cause of autism?
13 A No.
14 Q I'd like to now ask you a few questions
15 about the Lopez-Hurtado article that the Petitioners
16 have discussed. This is at Petitioner's Master List
17 446. Have you had a chance to review that paper?
18 A Yes, I have.
19 Q Do you know what journal that article was
20 published in?
21 A It's the American Journal of Biochemistry
22 and Biotechnology.
23 Q Have you ever read an article published in
24 that journal?
25 A No.

1 Q Did you try to find this article on your
2 own?
3 A Yes, I did.
4 Q Where did you look for it?
5 A I looked through the entire Harvard Medical
6 School Library System.
7 Q Did you look anywhere else for it?
8 A No.
9 Q Did you find it in the Harvard --
10 A No.
11 Q Does the absence of the journal, or the fact
12 that you couldn't find the journal at the Harvard
13 Medical School Library indicate anything to you about
14 the significance of this journal?
15 A Well, they have the second largest library
16 in the country. For some reason it didn't carry it.
17 Q The Lopez-Hurtado study, what areas of the
18 brain did the researchers look at?
19 A They were interested in speech-related
20 areas. Area 44 is part of Broca's area, which is the
21 motor speech area. The back end of Area 22 is I
22 presume, they call it Bernache, and the top end of the
23 superior temporal gyrus is the angular gyrus, Area 39,
24 and those are the areas that they looked at.
25 Q Why would these areas be of interest to

1 these researchers?
2 A Because of the involvement of language
3 dysfunction in autism.
4 Q Could you briefly summarize what results the
5 researchers have reported in this study?
6 A In general they reported, they thought there
7 was a decreased number of neurons, increased number of
8 glial cells, and accelerated lipofuscin accumulation.
9 Q Did you review the methodology that these
10 researchers applied?
11 A Yes, I did.
12 Q Did you identify any problems with their
13 methodology?
14 A Yes. I thought there were some problems
15 which, some things which are not addressed which are
16 problems.
17 Q Could you give some examples of those
18 problems?
19 A On the critically referred journals, they
20 will want those areas carefully specified, and to be
21 dead sure that they're in that area rather than just
22 taking a block from some place and assuming it's
23 there. So without proper cyto architectonic
24 definition of the area you can't be sure that each one
25 of those measurements was made in the same place.

1 That's of cell types and cell density. The
2 other problem is that the lipofuscin pigment varies
3 from cyto architectonic area to cyto architectonic
4 area which is another reason to be certain that you're
5 in the proper area. There's no assurance in the paper
6 that they had done that.
7 Q And were there any problems with the cell
8 counting methods?
9 A Yes, there were. That method would not be
10 accepted in any of our critically referred journals.
11 Q Dr. Kemper, did the Lopez-Hurtado study
12 microglia?
13 A No.
14 Q How can you tell that it didn't?
15 A Didn't mention it.
16 Q What were the researchers staining for in
17 that study?
18 A They stained for standard stains for which
19 they measured neuron densities, and possibly glial
20 cells. They also stained with GFAP which is a
21 specific stain for glial cells, and they stained for
22 lipofuscin pigment.
23 Q So when this paper refers to glia in the
24 result section, is it fair to say they may be
25 referring to astrocytes by the term glia?

1 A I would presume so, the way it's written,
2 yeah.
3 Q So this study really doesn't tell us about
4 microglial activation that was reported in the Vargas
5 study?
6 A No.
7 Q This paper reports decreased neuronal
8 density in two brain areas. You may have already
9 touched on this, but do you believe the methods used
10 in the study were appropriate for assessing neuronal
11 density?
12 A No, I do not.
13 Q Given the flaws in the cell counting method
14 that you identified, how much confidence do you have
15 in the results of this paper?
16 A It's a very interesting idea and I would
17 like to see it done with proper technique.
18 Q This paper also reports increased density of
19 astrocytes. Would that finding, supposing it's
20 correct, be compatible with astrocyte death?
21 A No.
22 Q Doctor, in your opinion, would this paper be
23 accepted in a reputable journal?
24 A No.
25 Q Does this study in any way add to the work

1 performed by Drs. Pardo, Vargas and Zimmerman?
2 A No.
3 Q Would you personally rely on this study for
4 information about the neuropathological basis of
5 autism.
6 A No, I'd be very careful about it.
7 Q Doctor, just to wrap up, I want to summarize
8 your opinions on Dr. Kinsbourne's neuro inflammation
9 hypothesis.
10 First of all, do you believe that microglia
11 are damaging the brain in autism?
12 A No.
13 Q What is your main reason for that belief?
14 A Its role in the neuro immune response which
15 according to them is very consistent with widespread
16 defects in brain development that we had noticed.
17 Q And do you believe it more likely than not
18 that microglia are destroying astrocytes in autistic
19 individuals?
20 A No.
21 Q What is your main reason for that belief?
22 A There's no evidence for the loss. No good
23 credible evidence for the loss.
24 Q Do you believe it more likely than not that
25 astrocytes are dying in autistic individuals?

1 A I don't believe that.
2 Q And do you believe it more likely than not
3 that astrocytes are inactive in autistic individuals?
4 A The literature is quite the reverse.
5 Q Do you believe that the roles of microglia
6 and astrocytes in autism are more likely than not
7 explained by prenatal factors?
8 A Yes.
9 Q Do you believe that Dr. Pardo's work
10 supports Dr. Kinsbourne's mechanism of postnatal neuro
11 inflammation as the cause of autism?
12 A No.
13 Q Do you believe that neuro inflammation is a
14 likely explanation for any of the structural changes
15 that you and others have observed in the brain of
16 autistics?
17 A Yes.
18 Q You believe that neuro inflammation is the
19 cause of those changes?
20 A No. I'm sorry. I must have --
21 Q All right, let me make sure the question is
22 clear.
23 Do you believe that neuro inflammation is a
24 likely explanation for any of the structural changes
25 you and others have observed in the brains of autistic

1 individuals.

2 A No, no. I'm sorry.

3 Q Do you believe it is more likely that any

4 neuro inflammation that may be present in the brains

5 of autistics is a response to the developmental

6 abnormalities you and others have observed in the

7 brain of autistics?

8 A Yes.

9 Q And do you hold the opinions that you stated

10 here today to a reasonable degree of scientific

11 certainty?

12 A Yes, I do.

13 MR. JOHNSON: I have nothing further.

14 SPECIAL MASTER VOWELL: How much time would

15 you like, Mr. Powers?

16 MR. POWERS: Five minutes.

17 SPECIAL MASTER VOWELL: Simply to get your

18 slides up?

19 MR. POWERS: If we say bottom of the half

20 hour, then maybe that's seven or eight minutes, but if

21 we did it at 2:30?

22 SPECIAL MASTER VOWELL: Sure. We're in

23 recess until 2:30.

24 (Whereupon, a recess was taken).

25 SPECIAL MASTER VOWELL: Let's go back on the

1 record.

2 Mr. Powers, would you begin your cross-

3 examination?

4 MR. POWERS: Yes.

5 Good afternoon, Dr. Kemper. My name is Tom

6 Powers and along with Mr. Williams I'm representing

7 the Petitioners' Steering Committee and both William

8 Mead and Jordan King.

9 THE WITNESS: Okay.

10 CROSS-EXAMINATION

11 BY MR. POWERS:

12 Q A couple of things to ask you about from

13 early in your testimony.

14 You testified that neuropathology was

15 important both to understanding the etiology of autism

16 and to the diagnosis of autism. This was in response

17 to the government lawyer's question.

18 Can you explain what neuropathological

19 findings are currently used to diagnose autism

20 spectrum disorder?

21 A You have to clarify that. You mean

22 techniques?

23 Q You're the one that testified that

24 neuropathology was useful to diagnosing autism. And

25 in response to a question about whether it was --

1 MR. MATANOSKI: I understand that that
2 actually wasn't the question.
3 MR. POWERS: That is my recollection. We
4 can look at the transcript, but --
5 SPECIAL MASTER VOWELL: Just go ahead and
6 ask the question, and if it's not what he said, he'll
7 tell you that.
8 BY MR. POWERS:
9 Q You were asked a question if neuropathology
10 was helpful in both, and this is what I wrote down in
11 quote marks, it was helpful "in the etiology and
12 diagnosis of autism."
13 So my question to you is, what
14 neuropathological findings are used to diagnose autism
15 spectrum disorders?
16 A The diagnosis of autism is a clinical
17 diagnosis. It is not a pathological diagnosis.
18 Q So your testimony is that neuropathology is
19 not something that would be used to diagnose autism,
20 correct?
21 A That's correct.
22 Q That saves me having to use the DSM-IV
23 criteria. I appreciate the answer.
24 A I try my best.
25 Q You also were asked a question about how

1 many total brains, how many actual brains of people
2 have been used in this long series of
3 neuropathological studies involving autism. How many?
4 A I've got the numbers here. I'll give them
5 to you. I knew you'd ask that.
6 Our own series is nine. The Hutsler --
7 Q Excuse me. When you say series, so you have
8 nine brains --
9 A We have nine that we've examined.
10 Q And that generated the series of papers. I
11 just want to -- when you say series, it's a series of
12 papers.
13 A That's correct.
14 Q Hutsler is eight.
15 Bailey is six.
16 Those are the series. There are individual
17 case reports as well, but those were the series.
18 Q And the first series was published 1994, was
19 that the first one?
20 A No. The first case of ours was '85.
21 Q So in the series of papers that you're
22 talking about there are 23 individual brains that are
23 represented by this long series of papers by multiple
24 authors.
25 A That's correct.

1 Q So whatever findings one would want to
2 extrapolate from those 23 individual brains would then
3 be what you're using to apply across the entire
4 population of people with autism, correct?
5 A Well, they are examples and they were
6 randomly collected. There was no special reason to
7 collect them other than the fact that they had autism.
8 Q Do you have an idea from the time that you
9 started doing the publication of these series to the
10 present, how many people with autism are there in the
11 United States?
12 A Eric Fombonne is going to testify about
13 that, but the current CDC number is one in 156, I
14 believe.
15 Q As has been demonstrated in the past, I'm
16 not the math whiz, but in a population of some 300
17 million people, if one out of 156 has autism, we would
18 be talking about several millions of people with
19 autism.
20 A Okay.
21 Q So these 23 brains then that we're talking
22 about are a sample out of many millions of people. Is
23 that a fair statement?
24 A Yes.
25 Q In describing the neuropathology that you

1 and other authors have identified here, is there
2 anything about a living person that you can learn -- I
3 should actually reverse that.
4 If you look at a living person with autism,
5 aside from doing a brain autopsy is there any other
6 way to get a picture of the neuropathology of that
7 living person with autism?
8 A Yes.
9 Q How can one do that?
10 A With MRI scans, would be one way to do it.
11 Q What are the other ways to do it?
12 A Well, I suppose there are ways to look at
13 organization with functional MRIs, with PET scans. Is
14 that what you mean?
15 Q I'm just looking for -- My question is,
16 aside from autopsy, is there any way that one can take
17 an autistic individual and learn the neuropathology in
18 that individual?
19 A I'm sorry. I understand you now.
20 The resolution of these other techniques is
21 such that it's very unlikely that you'd pick them up.
22 Q So it's unlikely that imaging is going to
23 pick them up. You'd actually have to have tissue.
24 A There are some that they do pick up, but
25 nothing with the detail that I show here.

1 Q And the detail that you showed, this is the
2 detail at the cellular level, correct? Purkinje --
3 A That's right.
4 Q Granular cells.
5 A Right.
6 Q These discreet sections you would actually
7 need tissue biopsy to get that level of detail, is
8 that correct?
9 A I don't know about biopsy but --
10 Q Autopsy.
11 A Autopsy.
12 Q So the imaging wouldn't capture it. That's
13 all I'm trying to establish.
14 A I don't think so. They've tried, but it's
15 not really good.
16 Q So short of autopsy there really is not any
17 way to look into the brain of an autistic person to
18 get an idea of what pathology is involved, correct?
19 A I would say so. For brain size you can do
20 it, but the others, not.
21 Q Brain size, that's typically going to be
22 measured by head circumference, is that correct?
23 A It depends on how old you are.
24 Q How does it depend? Explain that please.
25 A I'm not too sure where the age cutoff is,

1 okay? So you can work on me on that. But in young
2 children you can measure it with a tape and there's a
3 very good correlation between head circumference and
4 brain size. And then later in development, I'm not
5 sure exactly where the cutoff is, that becomes
6 unreliable.
7 Q And when you say it becomes unreliable, are
8 you saying that head circumference is no longer a good
9 surrogate for actually capturing the brain volume?
10 A It's a very accurate way early on.
11 Q I understand the early on, but I just want
12 to make sure what we're talking about.
13 As a person gets older --
14 A It's less accurate. That's very nicely laid
15 out in the Redcay and Courchesne paper.
16 Q Now there have been a series of studies done
17 that looked at head circumference and head growth
18 patterns among children. Are you familiar with those?
19 A Normal or autistic?
20 Q Autistic. These are the ones you cited in
21 your report.
22 A Of course.
23 Q In looking at some of those studies there is
24 some effort to describe a general pattern and a
25 general trajectory of brain growth.

1 A That's right.
2 Q Do you recall those types of efforts?
3 A Yes.
4 Q And when one looks at the individual
5 studies, Hazlett, which is the 2007 study that you
6 cited in your report, my recollection of Hazlett was
7 that the controls and the cases, that is the autistic
8 cases, were roughly the same until a year and then
9 they diverged at 12 months. Do you remember that?
10 A No, I don't remember that detail. I used
11 the Hazlett paper mainly for other reasons, but I have
12 my notes on it here if you want them.
13 Q I thought I brought your report up here.
14 A What did I say?
15 Q What you say in the report, and this is on
16 text page four. We're pulling it up on the screen
17 here in just a moment.
18 On page four, that very last full paragraph
19 is the paragraph --
20 A Yes. I know where --
21 Q Excuse me, Doctor, you're speaking -- Wait
22 until I ask you a question because we're going to talk
23 over each other and it's going to be impossible for
24 the record to be clear and I'll try to do the same for
25 you. I'll do my best not to interrupt you.

1 If we could highlight the last full
2 paragraph on page four, and the first words there are
3 "Several studies have".
4 A I've got that.
5 Q We're going to get the highlight up for the
6 whole paragraph. That just makes it easier to read.
7 Doctor, if you see Hazlett there discussed
8 initially it says that "Reported head circumference of
9 the autistic individuals began to diverge at 12 months
10 of age."
11 A That's right.
12 Q Did I capture that correctly then when I
13 said --
14 A That's right.
15 Q -- from birth to 12 months the controls and
16 the autistics were close together, and then they
17 diverted at 12 months.
18 A In this study, that's right.
19 Q In this study.
20 The Dawson study, the 2006 study which was
21 discussed, take a look at that.
22 A Oh, there it is. Yeah.
23 Q Look up after you've finished reading the --
24 A Okay.
25 (Pause).

1 A Yeah.

2 Q What Dawson reports is actually that the
3 differences were confined to the first 12 months.

4 A That's what Jerry says, yeah.

5 Q So you've got one study that says they're
6 the same in the first 12 months and then diverge; and
7 this one says any differences are confined to the
8 first 12 months.

9 A That's right.

10 Q If we go to Dr. Courchesne, his 2003 paper,
11 let's take a look at that. It continues to the next
12 page, I believe.

13 A That's the one that I showed here.

14 Q Right. You discuss that in your slides.

15 A That's right.

16 Q In there, he sees no statistically
17 significant increase at three to five months, but a
18 significant increase at six to fourteen months.

19 A That's correct.

20 Q A different result than you see in Dawson,
21 and a different result than you see in Hazlett, right?

22 A That's correct.

23 Q Now Dementieva, is the next one if you
24 continue on. We're actually on page five of your
25 report now. Do you see that reference there to a

1 "sudden and excessive increase at one to two months"?
2 A That's right. Yeah.
3 Q So you've got these four different studies
4 --
5 A That's right.
6 Q -- with results that are divergent and
7 sometimes conflicting, correct?
8 A That's correct.
9 Q So the diversity in these head studies is
10 further discussed in what is the Respondent's Exhibit
11 289. This is the head circumference and height in
12 autism study. This is Dr. Lainhart. I believe you
13 refer to this --
14 A That's right, I refer to that paper.
15 Q We've got that cover page up on the screen.
16 Susan Folstein, is she a colleague of yours?
17 A I know her. I know Susan.
18 Q Okay. Does she work at Boston University as
19 a neuropathologist?
20 A No, no. She's not. She was at Tufts
21 University and now she's I think in Florida.
22 Q In this study, if we look on the very front
23 page --
24 A Yeah.
25 Q Excuse me. That is not the page I wanted to

1 look at. If we look at Exhibit page 16 out of 18 --
2 A I don't have that paper in front me I don't
3 think.
4 Q Sorry.
5 A Thank you.
6 Q Doctor, there are two different page
7 numbers. I'll help guide you through this.
8 A Okay.
9 Q At the very bottom there is an exhibit
10 stamp, page number. Do you see that?
11 A Yes.
12 Q That's what I'll refer to then, instead of
13 the text of the journal. It's page 16 of 18.
14 A Okay. This is the end of it.
15 Q There's a heading called implications.
16 We're going to go ahead and zero in on the first half
17 of the paragraph on the right hand column of the page.
18 Under implications.
19 What the implications of the study are, that
20 there's a very wide distribution of head circumference
21 among people with autism. Correct?
22 A Yes.
23 Q They say that the diversity of head
24 circumference data reflects potentially the diversity
25 of the clinical presentation symptoms. Correct?

1 A I don't remember the correlations with the
2 clinical features. Just off the top of my head.
3 Q And we're not going to go through the
4 tables, but what they do talk about is the increased
5 variance of distribution, that is of the head
6 circumference, underscores the clinical heterogeneity
7 of autism. Is that your recollection of what the
8 study stands for?
9 A Yeah, that was one of their conclusions.
10 Q It talks about, in that same paragraph, the
11 dimensional features of autism. One of the
12 dimensional features of autism, would that include the
13 time of onset of autism?
14 A That I don't know.
15 Q Is time a dimension?
16 A Yes.
17 Q Would time in the progress of a disease be
18 an important consideration in studying that disease?
19 A Yes, of course.
20 Q Is there anything in this paper suggesting
21 that head circumference data was collected
22 specifically on children with regressive autism?
23 A No.
24 Q In any of the studies that we've talked
25 about has there been any data collected on children

1 specifically with regressive autism? Aside from
2 Vargas, which you mentioned earlier.
3 A No.
4 Q In the 23 brains that you described upon
5 which neuropathological published research is based,
6 do any of those brains have specific information about
7 whether the subject suffered from regressive autism or
8 not?
9 A No, not in the autopsy series.
10 Q There was no information about the severity
11 of the symptoms of autism?
12 A There is information on severity, yes.
13 Q What information is there generally on the
14 severity?
15 A In particular the cases of Bailey are much
16 more severe than the others.
17 Q In Bailey or anybody else is there any
18 information for those particular brains about the age
19 of onset of the symptoms?
20 A I have not looked at those papers for that
21 issue.
22 Q Also in that study, there's one other note I
23 think I wanted to run by you. Actually, that was it
24 so we can put that aside and save you that reading.
25 I want to switch to the slide presentation

1 that you were walking us through earlier.
2 If you look on page, I guess this is Trial
3 Exhibit 10. I think we're at page four. This is the
4 template of developmental events.
5 A Yeah.
6 Q In looking at this there's a very large
7 scale for events that happen in the approximately 40
8 weeks of gestation from conception to birth.
9 A That's correct.
10 Q So about two-thirds of the chart is related
11 to that, correct?
12 A Yes.
13 Q After birth the only thing that's listed is
14 a compression of the first four years and a vertical
15 line that says abnormal brain growth.
16 A Correct.
17 Q Certainly you don't mean to imply by this
18 chart that the only thing happening with brain
19 development after birth is abnormal brain growth?
20 A It's short so I could fit it on the page.
21 But no, there's no question, but there's a
22 considerable amount of brain growth. You can see your
23 own child grow up.
24 Q So after a child is born there's a
25 significant amount of brain development activity, the

1 brain is physically growing in size, correct?
2 A No question.
3 Q Synapses are being formed, correct?
4 A No question.
5 Q Synapses are being pruned so that they're
6 more functional correct?
7 A That's also correct.
8 Q Axons and neurons are migrating through
9 different regions of the brain to their final
10 destination.
11 A Sure. And some are being eliminated.
12 Q Pruning not just of dendrites on a cell, but
13 actually elimination of cells. The organization of
14 cells is going on, correct?
15 A Yes. It's mainly organization at that
16 stage, yeah.
17 Q This is a process that goes on certainly
18 through the first two years of life, correct?
19 A Oh, way beyond that.
20 Q That's why I said at least through the first
21 two years of life.
22 A Yeah.
23 Q A lot of that process is mediated by glial
24 cells, correct?
25 A Well, they're a part of the process because

1 they support the neurons, but the major thing is
2 neurons.
3 Q But the movement of neurons and the
4 organization of neurons, cells such as
5 oligodendrocytes and astrocytes play a significant
6 role, correct?
7 A In later brain development?
8 Q I'm talking about birth to two. Are you
9 referring to that as later brain development?
10 A No. I just want to know what you're
11 referring to.
12 Q Birth to two is what I'm talking about.
13 A Sure. There's a lot of development there,
14 especially the oligodendroglial cells.
15 Q Is that with the myelin sheathing?
16 A That's right, there's an explosion of them.
17 Q So all of this activity does rely to a
18 significant degree, wouldn't it be fair to say, on
19 properly functioning glial cells in a glial network,
20 correct?
21 A Oh, they have to function properly, yeah.
22 Of course.
23 Q And one could imagine that anything that was
24 interfering with the normal function of glial cells
25 during this first two years could affect the ultimate

1 neuronal, not just the glial end points, but neuronal
2 end points, correct?
3 A I would say it's a reasonable statement.
4 Q In going to page six in your slides, this is
5 a section of brain, this is I guess a very thin slice
6 that you put on a slide?
7 A Yes.
8 Q Is this stained?
9 A Yes.
10 Q What is it stained with?
11 A We call it Nissl stain. It's a stain from
12 the nerve cell bodies and the glial cell nuclei.
13 Q I couldn't hear the end.
14 A I'm sorry. It stains the nerve cell bodies
15 and the glial cell nuclei.
16 Q Can you see any glial cell nuclei in this
17 photograph?
18 A No. They're too small.
19 Q Is that a function of the stain or the
20 resolution of the microscopic work?
21 A It's certainly a function of the size. But
22 the astroglial cell you have to identify under fairly
23 high power in order to see them. They have very
24 specific criteria for their identification.
25 Q What would those criteria include to

1 identify glial cells and particularly astroglial
2 cells?
3 A The gold standard in that is actually stain
4 them with immunostains. And the immunostain is called
5 GFA, glial fibrialary acidic protein. That's the gold
6 standard for them. And that's the perfect way to do
7 it.
8 Q That's the gold standard because it's immune
9 reactive, correctly?
10 A Only with astroglial cells.
11 Q Right. So it doesn't stain the neurons
12 because it wouldn't have the immune cells on the
13 surface that would attract the stain.
14 A It wouldn't stain the other species of glial
15 cells either.
16 Q So in the slides that you have here on page,
17 actually I wanted to ask. On page eight is this one
18 of your slides or a collection of your slides?
19 A I'll look and see. Yes, it is.
20 Q Inferior olive --
21 A Yes, that's ours.
22 Q Was GFAP used in any of these?
23 A No. These brains, our own brains are
24 embedded in a substance called solodyn. It does not
25 allow for immunostains.

1 Q So the pathological slides that you've been
2 referring to here, none of the ones that are your
3 slides involve GFAP staining?
4 A That's correct.
5 Q And they were not at a resolution that would
6 pick up the astroglial cells, correct?
7 A Not at these.
8 Q Okay. I was curious, because as I went
9 through here there as a lot of talk of neurons, but I
10 didn't hear any discussion of glial cells in the
11 imaging.
12 A Pretty much what's known about, in the
13 proper science, pretty much what's known about the
14 glial cells is in that Vargas paper. Read our papers.
15 We've said very little about them. Because we didn't
16 want to make mistakes or say something that was wrong.
17 Q And you didn't say much about them because
18 it sounds like from just the basic workup of the
19 tissue, in a lot of ways you couldn't even look for
20 it, even if you wanted to, given the condition the
21 tissue was in and how it was preserved, you couldn't
22 have done the work, right?
23 A Right. I agree with you.
24 Q On page nine, and we're still in Exhibit 10
25 which is your collection of slides here.

1 A Yes.

2 Q These were the Purkinje cells. There was
3 some mention that you made of GABAergic. What's a
4 GABAergic neuron?

5 A It's an inhibitory neuron. That's the main
6 inhibitory transmitter in the brain.

7 Q And are Purkinje cells GABAergic?

8 A Yes, they are.

9 Q So Purkinje cells would be cells that would
10 excrete the neurotransmitter GABA which inhibits --

11 A That's correct.

12 Q So that's the main inhibitory
13 neurotransmitter in the brain, correct?

14 A That's correct.

15 Q Is it sort of the flip side of the glutamate
16 coin?

17 A Yes.

18 Q So if there is excess glutamate, GABAergic
19 cells such as Purkinje cells would be secreting GABA
20 to maintain homeostasis, so to speak. Is that
21 correct?

22 A You'll have to rephrase that because I'm not
23 too sure I follow you.

24 Q Okay.

25 If there was an excessive level of glutamate

1 in the brain, at any one time.
2 A Okay, for any reason. Okay.
3 Q For any reason. The feedback, the response
4 from the Purkinje cells would be to release GABA to
5 inhibit and bring homeostasis back --
6 A In balance, huh?
7 I don't know in particular whether the
8 Purkinje cells would do that. But the brain is filled
9 with GABAergic neurons. It doesn't have to be that
10 one.
11 Q But Purkinje cells are among the GABAergic?
12 A That's correct.
13 Q Are there other cells that are not neurons
14 that also release GABA and are GABAergic?
15 A That are not neurons?
16 Q Correct.
17 A I don't know of anything other than neurons.
18 Q Are there any forms of astrocyte that
19 release GABA into the extracellular space in the
20 brain?
21 A That's not in my expertise and I really
22 can't say that, but I don't think so.
23 Q I wanted to make sure again, just moving
24 through the slides. I suspect the answer but I want
25 to confirm it.

1 If we look at the imaging on Slide 12, the
2 inferior olive in childhood. And on 13.
3 A Yeah.
4 Q All of these inferior olive images are from
5 your lab?
6 A That's correct.
7 Q I ask because on most of these pages there's
8 a citation to whatever paper --
9 A That's right.
10 Q It's page 16 and page 17. Are those images
11 also from your lab?
12 A That's correct.
13 Q Are these all from those same nine brains
14 originally?
15 A No. We have a lot of studies going on in
16 the lab using immunostains and other approaches to
17 looking at the anatomy of autism. I do the
18 neuropathology for some of these studies. These are
19 found in those brains. These are frozen sections.
20 Q Again, this is not published in a paper
21 anywhere, this is just --
22 A No.
23 Q -- stuff from your lab?
24 A That's right. They're just nice examples.
25 And the cells in the white matter are shown by several

1 other people. It wasn't just me.
2 Q In the slides, and don't put it aside yet.
3 A Okay.
4 Q In the slides that you were just looking at,
5 the unpublished case control ones. In the staining on
6 those slides, did you do any of the immuno
7 histochemical analysis to identify glial cells?
8 A No. These are all done for
9 neurotransmitters.
10 Q So these were slides that are done to look
11 at the presence of what particular neurotransmitters?
12 A We're mainly interested in the GABAergic
13 system.
14 Q Was there any look in your work here that's
15 represented in the slides involving glutamate?
16 A As a matter of fact before I left to come
17 here I checked with the people because I knew that
18 somebody would ask that question. There's nothing
19 ready to publish on glutamate. The only possibility
20 is the, I'm not sure if it's published or not, is the
21 increase in MDA receptors in the granule cell layer of
22 the hippocampus. I'm sorry. Decreased.
23 Q In any of the work that you've done in your
24 lab, published or unpublished, have you ever looked
25 for neuro inflammation in the brains of autistic

1 people?

2 A No.

3 Q Let's talk a little bit about the Vargas,

4 the work that Drs. Vargas and Pardo were doing.

5 There's been discussion of a letter that was given to

6 us at the beginning of the hearing, and this is

7 Respondent's Exhibit LL. Do you have a copy of that

8 letter in front of you, Doctor?

9 A Yes, I do.

10 Q I was assuming you might. I first off

11 noticed that it is addressed to you. This is not

12 anything that was addressed to the Department of

13 Health and Human Services, or the Department of

14 Justice.

15 A That's correct.

16 Q This is personal correspondence between Dr.

17 Pardo and yourself.

18 A I presume so.

19 Q I'm just waiting for a yes answer so again

20 we can have that on the record. You've got to give a

21 full word answer.

22 A Okay.

23 Q This letter is dated May 13, but it

24 addresses a conversation that you had last year with

25 Dr. Pardo.

1 A That's correct.
2 Q In reading Dr. Vargas' paper, the one that's
3 entitled Neuroglial Activation and Neuro Inflammation
4 in the Brains of Patients with Autism. And we're
5 going to go ahead and give you a copy of that so you
6 have it on the desk.
7 A I've got the Vargas paper her.
8 Q Yeah, you're collecting some paper over
9 there.
10 This is Petitioner's Master Reference 69.
11 We're going to put that up on the screen. we're going
12 to replace the letter.
13 Is what you see on the screen there Doctor,
14 does that reflect the paper exhibit you have in your
15 hand?
16 A Yes, it does.
17 Q So we're all looking at the same thing.
18 I'm going to direct your attention to page
19 13 of the exhibit.
20 A Whose 13?
21 Q Where it says page 13 of 15 at the bottom.
22 A Got it.
23 Q We're going to look at the top left hand
24 corner of this paper. There's a sentence that begins,
25 "These observations do not support."

1 A Okay.

2 Q I'm going to blow that up. We're going to

3 highlight that up right through where it has Footnote

4 11. Do you see that?

5 A Yes.

6 Q So what the authors say is that the

7 observations they made don't support the previously

8 proposed hypothesis. That changes in the cerebellum

9 in autism result solely from developmental

10 abnormalities and olivary-cerebellar circuits and a

11 reduced number of Purkinje cells.

12 A Yeah.

13 Q Obviously I was just reading that from the

14 paper, but that's what it says.

15 A Fine.

16 Q Then if one turns to Footnote 11.

17 A I'm sorry, what are you saying?

18 Q There's a citation there to a paper.

19 A Oh, yeah.

20 Q It's Paper No. 11 which is on page 14 of 15.

21 A That's ours, that's right.

22 Q That's your paper?

23 A That's correct. Yeah.

24 Q So when this paper came out the authors were

25 saying our results are not consistent with this work

1 that Dr. Kemper and Dr. Bauman are engaged in.
2 A That's right.
3 Q Was it after this paper came out that you
4 had a conversation with these folks and said --
5 A No. No.
6 Q How did the conversation come about?
7 A He was at a meeting that I was attending,
8 that's the setting for it. And he had had this
9 wonderful paper here about the neuro inflammatory
10 response. I was just curious as to what he thought
11 about all of the developmental problems in the
12 autistic brains, and how he felt it fit in. That was
13 the substance of the conversation. It wasn't this
14 issue.
15 Q So it was more of a general conversation,
16 two scientists talking about where their work
17 overlapped.
18 A It was an interesting new concept and I
19 wanted to discuss it with the guy that was a key
20 player in it.
21 Q If you go a little bit further down on page
22 13 of 15.
23 A Yeah.
24 Q If we look on the left hand column, just
25 about halfway down the page there's a sentence that

1 begins, "The presence of MCP-1."
2 A I see that.
3 Q We're going to highlight that whole
4 sentence. The presence of MCP-1. It talks about, it
5 facilitates the infiltration and accumulation of
6 monocytes and macrophages in inflammatory central
7 nervous system disease, correct?
8 A I'm not a neuro immunologist. I really
9 couldn't speak from my own knowledge about that. I
10 only know what's here.
11 Q But what it does say here is that the neuro
12 immunologist thought it significant because this
13 particular proinflammatory cytokine facilitated the
14 infiltration and accumulation of monocytes and
15 macrophages in CNS disease. Correct?
16 A If that's what they say fine, yeah.
17 Q Monocytes and macrophages are immune cells,
18 correct?
19 A Yes, they're part of the adaptive immune
20 system.
21 Q They infiltrate into this inflamed area of
22 the brain because of the presence of the MPC-1,
23 correct?
24 A If that's what they say. As I say, I can't
25 really answer that from my own knowledge.

1 Q We're also then going to shift over to the
2 right hand side of that page. In the second full
3 paragraph there's a sentence that begins,
4 "Importantly, cells undergoing cell death."
5 A I see that.
6 Q I'm going to take a moment to highlight it
7 here on the screen. Let's go all the way down to the
8 sentence that begins, "Both proinflammatory." There
9 you go.
10 This substance that's being talked about
11 here, TGF-Beta 1. Do you have an understanding of
12 what that is?
13 A Only what's here. I really have no personal
14 involvement with any of these.
15 Q Would you trust me if I told you it was
16 transferring growth factor, Beta 1?
17 A Yeah, I know the name, yeah.
18 Q It's an anti-inflammatory cytokine, correct?
19 A That's my understanding of it, yeah.
20 Q The paper says that's the primary anti-
21 inflammatory cytokine that was found in these samples,
22 right?
23 A Okay.
24 Q The argument has been made, and I think it
25 was even expressed in your direct, that there are

1 protective pro-inflammatory cytokines released, and
2 you're relying on this paper for support of that
3 proposition, correct?
4 A Yes.
5 Q The authors of the paper do note that TGF-1,
6 while it is an anti-inflammatory, as it says, is
7 actually released by cells that are dying. Correct?
8 A That I don't know.
9 Q It says it in the paper. "Importantly,
10 cells undergoing cell death have been shown to secrete
11 TGF."
12 A Okay.
13 Q And they secrete it to protect bystander
14 cells, correct?
15 A That would be the same answer I gave before.
16 Q Your understanding then is if you have this
17 anti-inflammatory cytokine going on, while it may be
18 protective of some cells it's actually evidenced that
19 adjoining cells have recently died, correct?
20 A That's what they say. I don't know.
21 Q We're going to go on in this paper to page
22 14 of 15. If you look at the left hand column, the
23 first part of the section beginning, "The conclusion".
24 A Uh huh.
25 Q The authors here conclude that the

1 neuroglial reactions. First off, neuroglial describes
2 both the microglial observed reactions and the
3 astroglial reactions.
4 A That's my understanding, yes.
5 Q So they're talking about two different
6 groups of glial cells that they found were activated
7 in these brains, correct?
8 A That's my understanding, yes.
9 Q So that this neuroglial reaction, we've been
10 talking a lot about, or you've been talking a lot
11 about astrocytes. This neuroglial reaction also
12 involves the microglia, correct?
13 A That's correct.
14 Q The microglia are the cells we've heard
15 described as the macrophages of the brain, the brain's
16 innate immune system.
17 A Yeah. They have other functions too.
18 Q But in terms of the immune response, the
19 microglia cells in response to an antigen, a virus,
20 something like that, will react to eliminate the
21 invader, so to speak.
22 A They're part of the reaction, yeah.
23 Q So in the mechanism they describe, they say
24 that there are important mechanisms associated with
25 neural dysfunction in autism and that the cerebellum

1 is the focus of an active and chronic neuro
2 inflammatory process in autistic patients.
3 A Yeah.
4 Q That's what they conclude in the conclusion
5 section.
6 A Yeah, that's right.
7 Q Now they don't ascribe a particular cause at
8 that point to this neuro inflammatory process.
9 A No.
10 Q They don't say this is a neuro inflammatory
11 process that's limited to earlier pathological
12 conditions of these patients, do they?
13 A Well, that's one of the possibilities
14 Q So one of the possibilities is, as you
15 testified, that the neuro inflammation is related to
16 the pathology that exists that was essentially
17 prenatal in its origin, correct?
18 A I'm not sure is or can.
19 Q That's what I'm trying to get at. It can
20 be, but it is not necessarily so, correct?
21 A As I told you before several times, I'm not
22 an expert on this stuff and I don't really -- What I
23 know is what's in Pardo's letter, you know, and here.
24 Q I understand that. But you were asked
25 questions specifically asking what your understanding

1 and your opinion was having reviewed the studies in
2 the letter.
3 A That is my opinion.
4 Q So your opinion is that one of the
5 possibilities of this neuro inflammatory -- let me
6 finish the question.
7 A Sure.
8 Q Not to be snippy, but we've got to keep a
9 record.
10 A That's all right.
11 Q One of the possible explanations for this
12 neuro inflammatory process that they describe as
13 active, ongoing, one of the causes is pathology that
14 has its origins prenatally, correct?
15 A I would say likely.
16 Q It is also possible that this inflammatory
17 process reflects events that happened post-natally.
18 A I suppose so.
19 Q It's also possible that these neuro
20 inflammatory processes reflect a response to a toxin
21 or other environmental exogenous factor that could
22 have triggered the neuro inflammatory process. That's
23 a possibility.
24 A Well, they actually state there that they
25 don't think this response could be due to an exogenous

1 toxin, so I would just take --

2 Q Where do they state that? I'm just curious

3 as to where --

4 A Well I know. I know you would be curious.

5 (Pause).

6 A I'm not sure where I got that.

7 (Pause).

8 A I don't see it in here, sir.

9 Q So there's nothing in the peer-reviewed

10 published paper that rules out possible environmental

11 toxins as a cause of the observed neuro inflammatory

12 process, is there?

13 A I'd have to read it again.

14 Q And what you just read was Dr. Pardo's

15 letter, and there's nothing in that letter ruling it

16 out, was there?

17 A I didn't see it.

18 Q In fact if we turn to Exhibit 72 which is

19 another paper that Dr. Pardo and Dr. Vargas are the

20 authors of.

21 SPECIAL MASTER VOWELL: That would be

22 Petitioner's Master List 72, rather than Exhibit 72.

23 BY MR. POWERS:

24 Q Master Reference List No. 72. The lead

25 author on this one is Dr. Pardo. Do you have the

1 paper copy there, Doctor?
2 A Yes, I do.
3 Q Take a look at the screen. Make sure,
4 again, we're looking at the same document.
5 A Yes.
6 Q Let's go ahead and turn to page 9 of 12.
7 This is the exhibit page.
8 A I don't have one of your copies. But I've
9 got it here. That's the one with the diagram.
10 Q It's the one with the diagram. We're going
11 to look at a couple of things here.
12 Let's look at the text under "Conclusion",
13 and you see that that's highlighted.
14 A Okay.
15 Q If you take a look at that sentence, Dr.
16 Pardo here is hypothesizing that environmental factors
17 in the presence of genetic susceptibility and the
18 immunogenetic background of the host influence the
19 development of these abnormalities that they observed,
20 correct?
21 A That's what it says.
22 Q And it also attributes this hypothesis of
23 environmental factors specifically to the neuro
24 inflammatory changes responsible for the generation of
25 autistic symptoms, correct?

1 A Changes responsible, yeah.
2 Q So not only does Dr. Pardo's letter not rule
3 it out, it's specifically advanced as a hypothesis in
4 --
5 A Let me read this again.
6 (Pause).
7 A This generation of the autistic symptoms in
8 this sentence refers to the neuronal circuitry.
9 Q And the neuro inflammatory changes.
10 A Yeah.
11 Q So they hypothesize that environmental
12 factors could play a role.
13 A Yeah.
14 Q In fact if you look at the chart that's up
15 in the top left hand column, let's focus on that.
16 This is figure four on page nine in Petitioner's
17 Master Reference 72. There's actually a chart there
18 that it includes environmental factors in the
19 development of what is generated at the bottom right
20 hand there which is the autistic phenotype, correct?
21 A Yes.
22 Q And that under environment, toxins
23 specifically are mentioned, correct?
24 A Let me look at this. Yeah, toxins in the
25 environment.

1 Q Then under autistic phenotype, regression is
2 specifically listed, correct?
3 A Yes.
4 Q So this paper does postulate a hypothetical
5 role for environmental exposures in creating neuro
6 inflammation that ultimately leads to the regressive
7 phenotype of autism, correct?
8 A That can be an interpretation of this, yeah.
9 MR. JOHNSON: I have no further questions.
10 SPECIAL MASTER VOWELL: Redirect?
11 MR. JOHNSON: I have a few questions,
12 Special Master.
13 REDIRECT EXAMINATION
14 BY MR. JOHNSON:
15 Q Dr. Kemper, you were asked some questions
16 during cross-examination about brain development
17 during the first two years of life. Do you remember
18 those questions?
19 A Yes, I do.
20 Q And you were asked some questions about the
21 role of microglia and astrocytes and the development
22 of the brain. Do you remember those questions?
23 A Yes, I do.
24 Q First of all, are you aware of any evidence
25 that Thimerosal from vaccines affects that process of

1 brain development?

2 A I'm not aware of any evidence of that.

3 Q You're reviewed Dr. Kinsbourne's report,

4 right?

5 A Yes, I have.

6 Q Is that process of brain development, Dr.

7 Kinsbourne's hypothesis for how Thimerosal-containing

8 vaccines cause autism?

9 A I'm sorry, you'll have to -- It's too

10 complicated a question.

11 Q Is the process that you were being asked

12 questions about involving microglia and astrocytes and

13 their role in developing the brain.

14 A Yeah.

15 Q Is that what Dr. Kinsbourne is saying is

16 causing autism as a result of exposure to Thimerosal?

17 A Not to my understanding.

18 Q You were asked a series of questions about

19 your own work in the brains that you've looked at.

20 A Correct.

21 Q First of all, can you just describe a little

22 bit about how you look at slides and what that process

23 entails?

24 A In terms of the --

25 Q The process from when you get a brain sample

1 and how you go about looking at the samples.
2 Collecting the samples.
3 A If it's an autopsy we describe the brain and
4 we take blocks from it. Then it goes to the lab and
5 they process the tissues. Then we get back the
6 sections with whatever stains we think are necessary.
7 We look at them and figure out what we think is going
8 on and describe it and draw a conclusion.
9 Q How much of the brain do you look at?
10 A Maybe four or five blocks from a brain where
11 there are no complicated processes at all.
12 Q And how long does it take you to look at a
13 single section of the brain?
14 A Ten or 15 minutes, maybe.
15 Q But the process of looking at these, is this
16 a meticulous process?
17 A It depends on the nature of the changes. If
18 it's a complicated problem it just goes on for a long
19 time.
20 Q You were asked some questions about whether
21 you looked personally for neuro inflammation in the
22 samples that you've studied. Do you remember that
23 question?
24 A Yeah.
25 Q You testified that you did not look for

1 neuro inflammation. That's not been the focus of your
2 research. Is that right?
3 A Well yeah, those responses are not really
4 readily seen with our material.
5 Q But the Vargas group, they did look for
6 neuro inflammation, right?
7 A Yeah, with proper stains, yeah.
8 Q They found in their study that the astrocyte
9 activity was increased in their samples, correct?
10 A They were activated, yeah.
11 Q That is not, again, consistent with Dr.
12 Kinsbourne's hypothesis in this case.
13 A That's correct.
14 Q You were asked a series of questions about
15 the Vargas research and Dr. Pardo's letter.
16 Dr. Kemper, is Dr. Pardo, on the Vargas
17 article, is Dr. Pardo the senior researcher on that
18 study?
19 A That's my understanding.
20 Q And I believe you mentioned that during your
21 conversation with Dr. Pardo about a year ago at the
22 meeting you were at, did he say to you that he didn't
23 think it was a neuro toxin that was causing the neuro
24 inflammation?
25 A It could easily have been at that time. I

1 know I did hear it from him.

2 Q I think you said that you had read it

3 somewhere. I want to pull up the letter he sent you.

4 This again is Respondent's Exhibit LL.

5 If you look at the second paragraph on the

6 first page of his letter, and it's the highlighted

7 portion that we're pulling up on the screen.

8 This is where Dr. Pardo is talking about the

9 staining that they did and said that "These findings

10 are inconsistent with the hypothesis of a potential

11 toxic effect on astrocytes by neuro toxins or toxic

12 material."

13 Do you think that's what you were referring

14 to when you said you had read it somewhere?

15 A Yeah.

16 (Pause).

17 A "These findings are inconsistent with the

18 hypothesis of a potential toxic effect on astrocytes",

19 yeah.

20 Q So you think that could be what you were

21 referring to when you said you had read that somewhere

22 before?

23 A Yeah.

24 Q Is that a yes?

25 A Yes, I'm sorry.

1 Q During your conversation with Dr. Pardo did
2 you also discuss whether the findings of neuro
3 inflammation could be consistent with a response to
4 abnormal development?
5 A Yes.
6 Q That conversation, is that reflected in the
7 letter that Dr. Pardo has sent to you and submitted?
8 A Yes, it is.
9 Q And in your opinion, and based on your
10 almost three decades now of experience researching the
11 neuro pathology of autism, do you believe it is more
12 likely that neuro inflammation is a response to
13 developmental abnormalities that occur prenatally?
14 A Yes, I do.
15 MR. JOHNSON: Thank you. I have nothing
16 further.
17 SPECIAL MASTER VOWELL: Recross?
18 MR. POWERS: Yes, Special Master.
19 RECROSS-EXAMINATION
20 BY MR. POWERS:
21 Q Doctor, that sentence that you just read
22 from the letter, the one that, "This is confirmed by."
23 The final sentence says that, "These findings are
24 inconsistent with the hypothesis of a potential toxic
25 effect on astrocytes by neuro toxins or toxic

1 material", correct?

2 A That's right. Yes.

3 Q There's nothing in the sentence that says

4 that the astrocytes were unaffected by pro-

5 inflammatory cytokines released by microglia, correct?

6 A No, not in that sentence.

7 Q There's nothing in the sentence that says

8 the astrocytes were unaffected by reactive oxygen

9 species released by activated microglia --

10 A There's no mention to it at all.

11 Q Excuse me?

12 A There's no mention here at all of reactive

13 oxygen species.

14 Q So this just talks about the direct toxic

15 effect on the astrocytes of toxic material and neuro

16 toxins, correct?

17 A You're getting complicated for me now.

18 Q Let me back up and let me ask the question

19 this way.

20 A Please do, yeah.

21 Q The neuro inflammatory process, we discussed

22 this on my initial cross, involves both microglia and

23 astrocytes, correct?

24 A That's correct.

25 Q So the neuro inflammatory process generally

1 can be triggered by neuro toxins or toxic material, at
2 least to the extent that the microglia are involved,
3 correct?
4 A I suppose so, yeah.
5 Q And the microglia, if they are activated and
6 if they proliferate, they release reactive oxygen
7 species and they release pro-inflammatory cytokines,
8 correct?
9 A I really can't respond to that because it's
10 not part of my information.
11 Q Let me ask you if you know this. If
12 reactive oxygen species and pro-inflammatory cytokines
13 that are released in an inflammatory process contact
14 astrocytes, can they impair the function of astrocytes
15 or kill astrocytes?
16 A I have the same answer. I really can't
17 respond to that because it's not part of my
18 information.
19 Q Speaking of the information that we're using
20 here, I want to talk a couple of things.
21 As a scientist what you would rely on the
22 most I assume is peer-reviewed, published, scientific
23 literature, correct?
24 A That's correct.
25 Q So as a scientist reaching conclusions about

1 science, something that is in a peer-reviewed journal
2 article is going to carry the most amount of weight,
3 correct?
4 A It carries more weight for sure.
5 Q And if it's in a really good journal by a
6 really good author it carries even more weight.
7 A Obviously.
8 Q If you were engaged in a scientific inquiry
9 and were looking at non-peer-reviewed, non-published
10 material including personal correspondence from one
11 scientist to another, which do you think would be more
12 reliable?
13 A Well, I would have to depend on my opinion
14 of the scientist, really. If I was publishing it that
15 would be something different.
16 Q We're talking about a disinterested observer
17 resolving scientific facts.
18 A Yeah.
19 Q What would you rely on more? Personal
20 correspondence between people or peer-reviewed
21 published scientific journal articles?
22 A Well, yeah, the latter.
23 MR. POWERS: No further questions.
24 SPECIAL MASTER VOWELL: Apparently neither
25 my colleagues nor I have any questions for Dr. Kemper.

1 Doctor, you're excused.
2 We are now at not quite 3:30.
3 I wonder if it is possible, we have Dr.
4 Rodier as the first person on our list for tomorrow,
5 if we might get through her qualifications at least
6 today? That is her background publications. Before
7 we get into the substance of her testimony, and then
8 take up the substance tomorrow morning.
9 MR. POWERS: We'd stipulate to the
10 qualifications. Whatever the Special Masters and
11 Respondent want to do, but we're prepared to sit
12 through that part without any objection.
13 MR. MATANOSKI: Special Master, I don't
14 think there would be a problem doing that. I'm not
15 sure that tomorrow is going to necessarily be a day
16 that we need to --
17 SPECIAL MASTER VOWELL: You think tomorrow's
18 going to be a short day anyway?
19 MR. MATANOSKI: I don't think we're going to
20 be running up against 5:00 o'clock tomorrow, though
21 I'm not certain how long Dr. Goodman would go. I
22 don't think we would be pressed to get done tomorrow.
23 SPECIAL MASTER VOWELL: If there's no
24 difficulty with continuing today it may be more
25 appropriate to continue today. Given that tomorrow is

1 the start of a holiday weekend and some people drive
2 some distances home.
3 MR. MATANOSKI: I understand that. I guess
4 I was just thinking of our trial team. It's not a
5 three day weekend for them.
6 (Laughter).
7 SPECIAL MASTER VOWELL: Most of us I think
8 are taking things home with us as well.
9 MR. MATANOSKI: I understand from Mr.
10 Johnson who will be doing the direct examination of
11 Dr. Rodier, if she's ready he'd be ready to go through
12 her qualifications.
13 SPECIAL MASTER VOWELL: That would at least
14 take us a little further along the path.
15 MR. MATANOSKI: Yes, ma'am.
16 SPECIAL MASTER VOWELL: Okay.
17 Dr. Kemper, thank you very much for your
18 testimony. You're excused.
19 (Whereupon, the witness was excused).
20 SPECIAL MASTER VOWELL: Do you need a brief
21 recess before we begin with Dr. Rodier, or do you want
22 to just push on?
23 MR. MATANOSKI: I think we can just go right
24 on to Dr. Rodier.
25 Special Master, we may have to follow up

1 with a few questions tomorrow on qualifications.

2 SPECIAL MASTER VOWELL: We certainly

3 understand.

4 MR. MATANOSKI: Mr. Johnson is prepared for

5 that but he doesn't have it with him, so he's going to

6 do his best from memory.

7 MR. JOHNSON: And hope that your

8 qualifications match up similarly to Dr. Kemper's,

9 which I'm sure they do.

10 (Laughter).

11 MR. JOHNSON: We'll just go off of his

12 questions.

13 SPECIAL MASTER VOWELL: Dr. Rodier, would

14 you raise your right hand, please?

15 Whereupon,

16 PATRICIA M. RODIER

17 having been duly sworn, was called as a

18 witness and was examined and testified as follows:

19 DIRECT EXAMINATION

20 BY MR. JOHNSON:

21 Q Dr. Rodier, could you please state your full

22 name for the record?

23 A Patricia M. Rodier.

24 Q And Dr. Rodier, where do you currently work?

25 A I'm at the University of Rochester Medical

1 Center in Rochester, New York.
2 Q And what position do you hold at the
3 University of Rochester?
4 A I'm a Professor of ObGYN.
5 Q Could you briefly describe your educational
6 background and employment history leading up to your
7 current position starting with your college degree?
8 A I got my AB from Sweet Briar College in
9 Virginia, where I'm from; then went to the University
10 of Virginia for my PhD in Experimental Psychology.
11 After that I did a post-doc in the medical
12 school working in the field of embryology and
13 teratology.
14 Q What did you do after that?
15 A After that I stayed on the faculty of the
16 medical school for about ten years.
17 Q You mentioned teratology, and we've heard
18 some testimony about that earlier in the trial. I was
19 wondering if you could, explain what teratology is.
20 A Sure. I think everyone's heard of
21 toxicology and you've had a number of toxicologists
22 testify.
23 Teratologists are toxicologists who
24 specialize in the developing animal or human. In fact
25 in just the last few years we've changed the name of

1 the journal Teratology to Birth Defects Research. So
2 they're experts on birth defects.
3 Q That's closely tied to development, is that
4 true?
5 A Yes.
6 Q What responsibilities do you have in your
7 current position?
8 A For over 20 years I've been about 100
9 percent funded by NIH, so I don't have much in the way
10 of teaching duties or administrative duties. I'm just
11 mainly full time research.
12 Q What have some of your research interests
13 been over the years?
14 A Always I've been interested in the
15 development of the nervous system and how anything
16 that interferes with it might alter it so that you get
17 aberrant behavior. Since my PhD was in psychology, of
18 course I have an interest in behavior.
19 Initially I was interested in things like
20 learning disabilities and was interested in very basic
21 approaches to trying to figure out how the nervous
22 system changed over time and how that influenced the
23 outcome of injuries. So I worked with some sort of
24 classic teratogens like fibasticytodine and
25 fifluouroeuracil. These are actually things that at

1 the time were being thought of as possible
2 chemotherapy agents. And they're things that are
3 known to interfere with development very directly.
4 By doing that I developed a sense of, and a
5 lot of papers, on what difference it makes when an
6 injury occurs at one time versus another in
7 development.
8 Q Have you published any articles or texts on
9 your research?
10 A Yes.
11 Q Do you have an idea as to approximately how
12 many publications you have?
13 A I'm not really sure. I would say it's
14 probably like 60 or 70.
15 Q Are you a member of any professional
16 organizations?
17 A IMFAR and the Teratology Society, the
18 NeuroTeratology Society are organizations I've been a
19 member of.
20 Q Are you Board Certified in any areas?
21 A No, I'm not a physician.
22 Q So Board certification is not required.
23 A Right.
24 Q Are you a reviewer for any journals?
25 A Lots.

1 Q Can you name a few?
2 A NeuroTeratology and Toxicology, I'm on the
3 Editorial Board, and I've served as the President of
4 the Editorial Board of Teratology. But I also review
5 for Autism and Developmental Disabilities,
6 Developmental Psychobiology, Medical Genetics,
7 Biological Psychiatry, many different journals.
8 Q Do you in your research and the work that
9 you've done, have you had any, I don't want to say
10 exposure to mercury, but any experience working with
11 mercury?
12 A Yes. When I moved to the University of
13 Rochester in 1980 which is a big center for studies of
14 mercury in the Toxicology Department, I became
15 interested in why the unborn child was so much more
16 sensitive to methyl mercury ingested by the mother
17 than the mother herself. This was well known from the
18 accidents in Iraq.
19 So I set out with a graduate student to try
20 to figure out why that was. And we immediately
21 discovered something.
22 Q What did you discover?
23 A That methyl mercury causes arrest of cells
24 in mitosis. When cells are dividing they sort of
25 round up and they almost look like they have a star in

1 them, that's called starry metaphase. In the next
2 part of the process, those starry lines, which are
3 chromosomes, start to pull apart. You see something
4 that looks like this. Then you see the two cells
5 split in between.
6 There are drugs that do that. Colchicine is
7 the maine one. We were amazed to see that was what
8 was happening in our developing brains. We could see
9 starry metaphases everywhere. Then when we held the
10 animals longer and counted the number of neurons, we
11 had reductions in the number of neurons.
12 That process isn't going on to any great
13 extent in the brain of adults, so that explains the
14 greater sensitivity.
15 Q Are those findings, have they bene
16 published?
17 A Oh, yes.
18 SPECIAL MASTER VOWELL: Doctor, I'm going to
19 stop you. You were holding your hands with the
20 fingers pointing towards one another, sort in a cupped
21 or circular fashion, then you started pulling them
22 apart when you were saying "It looks like this," is
23 that correct?
24 THE WITNESS: That is how it looks.
25 If I had a pen I could draw you a picture.

1 SPECIAL MASTER VOWELL: Maybe we'll give you
2 one tomorrow.
3 BY MR. JOHNSON:
4 Q Dr. Rodier, you also have experience in the
5 field of autism as well, correct?
6 A That's right.
7 Q How did you become interested in the field
8 of autism?
9 A Because of my work on brain damage I've
10 often been invited to speak for groups like the
11 Learning Disabilities Association. And I was giving a
12 talk at a meeting a number of years ago and a parent
13 came up to me, the parent of an autistic child, and
14 said I think that those of you who work on development
15 really have something to offer to this field because
16 no one from development has ever looked at autism. At
17 first I thought well that can't be true. Then I
18 thought no, I think I know everybody in development of
19 the nervous system and they haven't. So I offered to
20 go home and do some reading for him.
21 I went home and read about 200 papers in a
22 couple of weeks. He was right. No one who works on
23 development had ever worked in autism.
24 So I definitely became interested. But in
25 my review of the literature I couldn't see enough

1 biological information that someone with my skills
2 could think of a way to introduce those to the field.
3 It was only later that year that I heard of the
4 discovery of the Thalidomide cases with autism, and
5 that made me realize how a teratologist could in fact
6 work on autism.
7 Q Do you remember approximately what year that
8 was?
9 A It was '83 or '84.
10 Q And since that time have you had an interest
11 in autism?
12 A Definitely.
13 Q Have you published specifically on the issue
14 of autism?
15 A Yes.
16 Q Can you describe some of those publications?
17 A One Dr. Kemper mentioned, I'm interested in
18 neuro anatomy, of course.
19 Q If you're going to discuss any of these
20 tomorrow you don't have to describe them in detail.
21 We've also looked at developing an animal
22 model of autism. Some of the discussion here has gone
23 into the fact that some of the animal model work has
24 not used behaviors in animals that can be shown to
25 have anything to do with the behaviors in autism. But

1 in fact we've worked at developing some behaviors
2 showing that they're different in human cases and then
3 taking them into animals that are behaviors that can
4 be done exactly the same in different species. One of
5 those is eyeblink conditioning.
6 So there are some behaviors. They're not
7 the kinds of behaviors that are used in diagnosis.
8 They're more neuro physiological measures. But we've
9 been trying to look for ones that might be good
10 parallels between the species.
11 Q You mentioned eyeblink conditioning. Could
12 you explain what that is?
13 A It's Pavlovian conditioning. You remember
14 that Pavlov would ring a bell and give his dogs meat
15 powder. After he rang the bell and gave them the meat
16 powder over and over, he would ring the bell and they
17 would salivate without the meat powder.
18 In eyeblink conditioning what you're doing
19 is delivering a little puff of air to the eye after a
20 tone comes on. The child or the adult, whoever,
21 blinks in response to the puff of air. After many
22 repetitions, they come to blink before the puff of
23 air, so that they protect the eye.
24 It's a wonderful measure because it's an
25 unconscious process. It requires no instructions.

1 With adults, you usually do it while they're reading a
2 book or a magazine. With our kids we'd do it while
3 they watched Shrek. So they're paying total attention
4 to the movie. They're not conscious of the air puffs
5 or the tones. But they quickly become conditioned, we
6 call it, they learn to blink following the tone.
7 Q This is a study that's currently ongoing in
8 your clinic?
9 A We've had studies going on actually in two
10 sites with this. Human ones at our place and animal
11 ones in Delaware.
12 Q And the goal of this study is to come up
13 with an animal model for what purpose?
14 A We've developed the animal model and we've
15 already done its neuro anatomy. But what we've done
16 now is we have been able to show that these animals do
17 have this oddity of eyeblink that we see in human
18 cases. so that's a parallelism that suggests that it
19 really is a good model.
20 So now what we'd like to do is take that
21 knowledge and look at some of the other animal models
22 to see if they are parallel to the human condition.
23 MR. JOHNSON: Special Master, I think that's
24 about --
25 SPECIAL MASTER VOWELL: About as far as

1 you're going to go today?

2 MR. JOHNSON: Right.

3 SPECIAL MASTER VOWELL: All right. Fair

4 enough.

5 I think we'll go ahead and excuse you for

6 the day, Dr. Rodier. We'll go off the record. We're

7 in recess until tomorrow morning at 9:00 o'clock.

8 (Whereupon at 3:43 p.m. the hearing was

9 recessed, to reconvene at 9:00 a.m. on Friday, May 23,

10 2008.)

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REPORTER'S CERTIFICATE

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

CASE TITLE: In Re: Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder or a Similar Neurodevelopmental Disorder;

HEARING DATE: May 22, 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: 5/22/08

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