UNITED STATES
COURT OF FEDERAL CLAIMS

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

Pages: 3001 through 3146/3230

Place: Washington, D.C.

Date: May 23, 2008

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SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

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

Friday,
May 23, 2008

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

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

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C O N T E N T S

E X H I B I T S

RESPONDENT'S EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
11	3009	--	Patricia M. Rodier Slide Presentation

P R O C E E D I N G S

(9:00 a.m.)

SPECIAL MASTER HASTINGS: Good morning to all. Please be seated. Before we begin today's testimony -- I see Dr. Rodier is back in the witness chair -- do we know yet what the general schedule is with Dr. Goodman?

MR. MATANOSKI: Yes, sir. He is going to be available this morning, so we anticipate as soon as Dr. Rodier's testimony is done, we'll move on to -- with a short break to make the change, we'll move on to Dr. Goodman.

SPECIAL MASTER HASTINGS: Very good. Anything we need to take care of before we --

MR. POWERS: Not from the Petitioners, Special Master.

MR. MATANOSKI: Nor from the government, sir.

SPECIAL MASTER HASTINGS: Okay. Very good. With that, Dr. Rodier, you've been sworn. You're back in the witness chair. Mr. Johnson, please continue with your examination.

MR. JOHNSON: Thank you, Special Master.

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Whereupon,

PATRICIA M. RODIER

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

FURTHER DIRECT EXAMINATION

MR. JOHNSON: Good morning, Dr. Rodier.

THE WITNESS: Good morning.

BY MR. JOHNSON:

Q We made it through some of your qualifications yesterday. There were just a couple of other points --

(Music plays.)

SPECIAL MASTER HASTINGS: InterCall operator, are you there?

INTERCALL OPERATOR: You're in the room. You're ready to go.

SPECIAL MASTER HASTINGS: Okay, thank you very much.

Please go ahead, sir.

MR. JOHNSON: Thank you.

BY MR. JOHNSON:

Q Dr. Rodier, as I was saying, we discussed some of your qualifications yesterday, but there were just a couple of points that I wanted to get into the

record. First, did you receive any honors or awards in connection with your Ph.D.?

A Yes. I was lucky enough to be a Woodrow Wilson fellow, and that was a national competition that paid for your graduate school for a few hundred people in the U.S.

Q And the second point that I wanted to cover is, do you have any NIH grants?

A Yes, I have two.

Q And what are they for?

A They are both for work on autism. The title of the first one, which I've had for 10 years, is "Genotype and Phenotype of Brainstem Injury in Autism," and that's a program project grant that involves a number of different universities and some foreign sites, and the second one is called "Genotype and Phenotype of Treatments of Autism," -- or "Response to Treatments of Autism," and that's a center grant that provides infrastructure and funds projects in my group at the University of Rochester.

Q And how much are those grants for approximately?

A About two-and-a-half million a year.

Q And do you have anybody working with you on these grants?

A Yes, many, many people. There are about 30 or 40 people at the M.D. or Ph.D. level who are supported by those two grants.

Q And those would be individuals that you are supervising --

A Yes.

Q -- on their work in these projects? Dr. Rodier, have you ever testified in a legal proceeding before?

A I have testified in writing. I've never testified in person.

Q Meaning that you've submitted reports or affidavits, but you actually --

A Yes.

Q -- haven't testified? What cases have you submitted reports in?

A The Canadian Omnibus which was on the same subject as this one, and the Redfoot case last year.

Q And was that a civil case?

A Yes.

Q And you said you hadn't testified. Is there a reason that you didn't testify in those proceedings?

A Both of those cases were dismissed before trial.

Q Doctor, turning to your second slide -- and

let me distribute those.

SPECIAL MASTER HASTINGS: I assume we should mark this as Respondent's Trial Exhibit No. 11.

(The document referred to was marked for identification as Respondent's Exhibit No. 11.)

BY MR. JOHNSON:

Q Doctor, looking at slide 2, can you briefly summarize the opinions that you are going to be giving here today?

A Yes, and I should say that we negotiated what I would talk about because there are so many experts, and I didn't want to overlap with what they were testifying about. So I think I am the only person actually in the country who has ever worked on both autism and mercury poisoning, and so I want to first revisit for you the Bernard paper of 2001, which is the only reason all of us are here today, because it claimed that the symptoms of mercury poisoning were the same as those of autism.

And then the second topic that I want to talk about is, when does autism begin? Is it initiated prenatally or postnatally?

Q And turning to slide 3, Doctor, you mentioned the Bernard article, and for the record,

this is Petitioners' Master List No. 262. Doctor, to the best of your knowledge, is this article essentially where the hypothesis that thimerosal causes autism started?

A Yes.

Q As a scientist who works in the area of autism, do you have any criticisms of the Bernard paper?

A I have many that are shared by scientists who work on autism and scientists who work on mercury, and there is one published article replying to the Bernard article, and it's by two experts on autism, Nelson and Bauman, and what they were criticizing in the article was the selection of symptoms, what the authors called the symptoms of autism, which included many things that occur in everyone; for example, nausea, vomiting, irritability, temper tantrums. Those are not diagnostic symptoms of autism. They are things that happen to people with autism, but they happen to all of us.

So they are not useful either for diagnosis or for comparing autism to other disorders. And they also included a lot of symptoms of autism, as they called them, that were ones that occur in many people, and in some cases with autism. So, for example,

mental retardation, depression, abnormal gait, these are things that are not normal like irritability and vomiting, but they occur in many conditions, not necessarily in autism.

They are not diagnostic symptoms, and so they can't be used to compare the symptoms of autism to the symptoms of another disorder.

Q And turning to slide 4, as a scientist who has done research with mercury, do you have criticisms of the Bernard paper?

A Right. When experts on mercury read this paper, what they are struck by is that the symptoms of what they call mercury poisoning have been drawn from cases of exposure to mercury vapor, which causes Mad Hatter's syndrome, and they've been drawn from exposures to inorganic mercury, which causes acrodynia, and also from both pre- and postnatal exposures to methylmercury, but there are very few references to ethylmercury, which would be the only kind of mercury poisoning that's relevant in this case, or to their hypotheses.

Q Because that's the form of mercury that's present in thimerosal?

A That's right.

Q Doctor, does the Bernard paper provide

support for the claim that mercury toxicity and autism share similar symptoms?

A No. Well, I mean, it purports to, but I want to show you examples of the kinds of comparisons they are making and instead of just giving you my opinions, let's just actually look at what they said, okay?

Q And right now we are referring to slide 5.

A Right. So, on the first line, marked No. 1, you will see that they say there are similarities in depression, depressive traits, mood swings, flat affect and impaired face recognition.

Q And, excuse me, just for the record, this is in the Bernard article, which is, again, at Petitioners' Master List 262. It's in Table 1 on exhibit page number 2. And if you can just tell us the significance of those citations.

A Yes, okay. Well, it's true that depression is a symptom of acrodynia, exposure to inorganic mercury. They are depressed because they are so sick and they have terrible pain in their hands and feet. It's true that mood swings are characteristic of Mad Hatter's disease. It's true that flat affect is a diagnostic symptom, actually, of autism, but impaired face recognition does occur in autism; it's never been

even tested in any kind of mercury poisoning.

So we have four examples here, and there is no overlap. The ones that are characteristic of different kinds of mercury poisoning don't occur in autism, and the ones that occur in autism don't occur in any kind of mercury poisoning. So you might think perhaps they don't really mean that the same symptoms occur, but just that all these symptoms are closely related, and so that means that the symptoms are alike, but that doesn't work either, because depression is not the same thing as mood swings, and flat affect is the opposite of mood swings, and impaired face recognition has nothing to do with mood, so these four things don't go together in any way.

And I'll just mention some of these others. Verbalizing and word retrieval problems do occur in Mad Hatter's disease, but echolalia and word use and pragmatic errors have never been reported in mercury poisoning. They occur in autism. Echolalia is the tendency to generate speech that's repetitions of things you've heard, for example, radio jingles or songs, or something that someone said to you.

So, for example, in one of the cases that we studied at Rochester, a little boy about 3 decided that he didn't want to be tested anymore and so he ran

toward the door, and his father ran after him and scooped him up and said, bet you want to get out of here, buddy. And of course, that's exactly what he wanted to do. So his father brought him back into the examining area, and he made a couple more escape attempts, but each one, he shouted, bet you want to get out of here, buddy, as he did it. But he's parroting instead of generating his own language.

Word use, there are many classic examples of problems with word use in autism, and they occur even in people with very high functioning autism or people with Asperger's syndrome, who may have normal vocabularies and high IQs, but they use words in odd ways, and the most famous example of this, I think, is a young man who described a hole in his sock as a discontinuity of knitting.

So he knows what the words mean, and they are not really inappropriate, but they are not used in the typical way. And of course, neither of these conditions has ever been reported in mercury poisoning. Then the third list I selected was 'lacks eye contact,' that is a symptom of autism but not of mercury poisoning; impaired visual fixation is a symptom of methylmercury poisoning, and it means that the brain control of the eye muscles is impaired, and

so the eye muscles aren't adjusting nicely to allow you to fixate on something.

Then, problems in joint attention occurs in autism, but it doesn't occur, as far as I know, in any kind of mercury poisoning, and it has nothing to do with vision. It's actually an example of a social impairment.

Q Did the authors of the Bernard paper also attempt to draw comparisons in biological abnormalities?

A They did, and --

Q And this is slide 6.

A So, for example, they pointed out that progressive microcephaly was characteristic of mercury poisoning -- that's methylmercury -- prenatal exposure, the children are born with small heads. I wouldn't call it progressive, but progressive microcephaly and macrocephaly they listed as symptoms of autism. Children with autism occasionally have microcephaly, but they are more commonly characterized by progressive macrocephaly, as we heard yesterday.

Macrocephaly, of course, has never been reported in mercury poisoning. Then they list that mercury poisoning causes demyelinating neuropathy. That's a chronic exposure to inorganic mercury does

cause that, but no one has ever reported that in autism. Then demyelination in the brain they list as a characteristic of autism, but no one has ever reported that in autism, and the reference they give says nothing about that.

Q And for the record, those examples were from Table 2 of the Bernard article, --

A Right.

Q -- which is exhibit page number 4 of that article. Doctor, if the authors of the Bernard article are trying to show a connection between thimerosal-containing vaccines and autism, why don't they talk about the symptoms of ethylmercury poisoning?

A One might well ask that question, and the answer is that it doesn't make a very good story if you compare the symptoms of autism to the symptoms of ethylmercury poisoning. So on this next slide, I've used an article by Zhang from 1984, and I --

Q And for the record, that's Petitioners' Master List No. 232.

A And the reason I picked this article is because Zhang actually studied, had the chance to study 41 people who had all been exposed to ethylmercury from tainted rice, and so they were able

to actually calculate how much they'd eaten. They knew what the dose was, in other words. They then examined them, followed the course of their disease, and were able to document their symptoms, and what they did was they actually counted how many of the people had symptom 1 and how many of the people had symptom 2, and the doses in this case ranged from very mild effects to death, and so they had a good range of different levels of symptoms to examine.

What they found was that the three most common symptoms were muscle weakness, loss of appetite, and dizziness. Those don't sound much like autism. The next 10 most common symptoms were nausea, abdominal pain and diarrhea, fever, numbness of the extremities, paresthesia and ataxia, vomiting, thirst, unsteady gait, ringing of the ears and headache, and again, I think you can see that none of these sound like any of the symptoms of autism that are used in diagnosis, so there is really no correspondence between the symptoms of ethylmercury poisoning and autism.

Q Now, Doctor, the Petitioners will argue that they are not claiming in this case that acute mercury toxicity causes autism, as hypothesized in the Bernard article. They will claim that their hypothesis is

that low levels of inorganic mercury persist in the brain and cause either oxidative stress or an inflammatory process which results in autism. Does that hypothesis make sense to you?

A No, it doesn't. I think earlier this week, one of the witnesses talked about the fact that scientists make every effort to try to disprove a hypothesis. They don't just look for support for a hypothesis, and at the time that this paper was written, and today, there is one piece of evidence that absolutely refutes the hypothesis that inorganic mercury in the brain causes any symptoms, and that is, the cases of acute poisoning with ethylmercury that have been documented to cause high, high levels of brain inorganic mercury in autopsy studies, that the people who were subject to those exposures -- they occurred in medical accidents and in the case of the tainted pork, which you've probably heard about, the New Mexico pork case -- in those cases, even though the people became seriously, seriously ill with very high levels of ethylmercury and corresponding high levels of inorganic mercury after the ethylmercury washed out, they all recovered completely from their neurological symptoms. After the ethylmercury was gone and they just had inorganic mercury, they no

longer had symptoms.

Q So the effects went away?

A Yes.

Q Doctor, now I'd like to turn to slide 8 and the next topic that you are going to address this morning, and that's the timing or when autism begins, and in your report, you identify five environmental risk factors for autism, and let me, now let's look at slide 9 and you can discuss those.

A Surely. The ones I've listed here are ones that come from population studies, and they are: exposure to rubella, thalidomide, valproic acid, which is a seizure medication, ethanol, and misoprostol, and to the right, I've listed the time that's the critical period when exposure has to occur for autism to be one of the results, and for rubella, that's before the ninth week after conception.

For thalidomide, it's week 3 and 4. Valproic acid, it's week 3 and 4. Ethanol, it's week 3 to 5, and misoprostol, it's week 6.

Q What can we learn from these studies? Does this mean that all environmental factors, when they are discovered, are all going to share the same period?

A It certainly doesn't mean that they have to.

Perhaps there are other times when an injury could lead to something like autism. For example, tuberous sclerosis cases don't show autistic symptoms early on, but as their brains become more and more injured from the tumors in their brains, they may show autistic symptoms. So there are probably other ways to produce those symptoms, but I think it's most likely that when, as we find more environmental factors or exposures that are involved, increasing the risk of autism, I think it's more likely that they will be in similar periods to this, in the first trimester.

Q Doctor, do you know what terbutaline is?

A Yes.

Q The Petitioners have raised the issue of terbutaline in this trial, and I was wondering why you didn't include terbutaline on your list of environmental risk factors.

A That's a good question. Because that study is actually a genetic study, the Connors study, and it is not a population study. That is, they didn't go out and find everyone they could who was exposed to terbutaline and then compare the rate of autism in those people to the rate of autism in the general population, as the studies I've listed for you did.

What they did instead was look for cases of

twins where one had autism, and then they looked in those twin pairs for the ones that had been exposed to terbutaline, and the pairs that had not been exposed, and what they were looking for was whether the end result as they grew up was that both twins had autism, or only the one twin had autism, and they were ascertained for one of the twins having autism, remember.

When they looked at their whole sample of cases, exposed to terbutaline or not, in this twin pairs, there was no significant increase in the second twin having autism in the whole set of cases. Then they cut it down another way and looked at a smaller subset and that was not significant either. They finally cut it down to a very small subset where both of the twins in the pair were male and they had no affected other siblings, and in that very, very small group, there were more concordant cases exposed to terbutaline. So the implication of that would be that terbutaline might have had an effect on those cases.

However, this study suffers from a problem that we have with all studies of things like optimality in delivery or pregnancy, and that is that it's very hard to tell whether the terbutaline caused the second twin to have autism or increased the risk,

or if whether, in fact, it was because the twin pairs that both had autism were threatening to be born too early, because that's the only reason to give them terbutaline.

So, is the terbutaline causing the effect or are the twins who are the most affected with autism being selected because of threatening to come too early?

SPECIAL MASTER VOWELL: Is what you are saying that the terbutaline preserved the pregnancy that would otherwise have been lost?

THE WITNESS: That's what it's given for.

SPECIAL MASTER VOWELL: I understand that, but then these twins are born, but had they not been given terbutaline, they might not have survived long enough to be diagnosed with autism in this period?

THE WITNESS: Right. I can give you an example from a paper that just appeared a few weeks ago in *Pediatrics* of the same problem, and that is, it was noted in this paper that children with very low birth weights have a higher rate of autism than children with normal birth weights, and that might mean that being born with a very low birth weight causes autism. It also could mean that an embryo and fetus that has autism is already injured, and so it

will have a smaller weight at birth.

So you can't separate the two, and that's the trouble with the terbutaline studies, so that's why I didn't include it.

SPECIAL MASTER VOWELL: That low birth weight study that you've referred to, has that been filed as an exhibit by either side?

THE WITNESS: No.

SPECIAL MASTER VOWELL: Okay.

THE WITNESS: It just came out a few weeks ago, so --

SPECIAL MASTER VOWELL: And does that study account for the length of gestation? I mean, is it low birth weight in children carried to term, or is it low birth weight because they were born early?

THE WITNESS: Actually, it's low birth weights because they were born early.

SPECIAL MASTER VOWELL: Okay.

BY MR. JOHNSON:

Q Doctor, the Petitioners have discussed a terbutaline rat study. It's the Zeratte study at Petitioners' Master List 106. Have you ever looked at that study?

A I've really just glanced at it.

Q In that study, weren't those rats given

terbutaline postnatally?

A Yes.

Q Would that be comparable to a postnatal exposure in humans?

A No, because they were given the terbutaline when they had just been born as neonates, and rats are born very immature compared to humans. You may know that their eyes haven't opened, their ears haven't opened, they have no hair, they are bare little red things, and so in fact, the period when they gave the terbutaline to those animals would correspond to late gestation in the human.

Q So humans who are exposed to terbutaline, is that a prenatal exposure or postnatal exposure?

A Prenatal.

Q Doctor, have you studied brain samples from autistic individuals?

A Yes.

Q What did you find in your studies? And we are now looking at slide 10.

A I found many things, but I just -- and I can tell you about those if you like, but I wanted to give you some examples of how histology can sometimes give us information about when an injury occurred, as well as showing us the pathology itself. And this is from

one of our studies at Rochester. On the left, you see a control brain, and -- do I have a pointer?

THE WITNESS: Would you mind if I just went over and stood by this screen? Can you see if I do that?

SPECIAL MASTER HASTINGS: Not at all. Please do.

THE WITNESS: Anatomists love pointers.

SPECIAL MASTER HASTINGS: Well, the problem is that I don't know if the microphone is going to pick you up.

THE WITNESS: I'm used to talking to a class of about 300 people. I think I can --

SPECIAL MASTER HASTINGS: All right, let's see if it works.

THE WITNESS: -- make myself heard.

Okay. In the control brain, what we are looking at is views of the facial nucleus, and this is the part of the brain that controls the muscles of facial expression, so smiling, closing your eyes, etc., and in the case of autism that we examined, that child had lack of facial mobility, and we looked at the facial nucleus to see if it were normal, and when you look at the control nucleus, what I want you to see is these black dots, those are the motor neurons

for the face.

There are about 120 of them in this picture. In the autistic case, there's only one at this level, but we counted the whole nucleus, and there were about 4,000 in this control case, and there were about 400, a little less than 400, in the case with autism.

But what I want you to see is the indication that this nucleus never existed, rather than having formed and then died in the person with autism, and here's what shows you that. This nucleus is defined, not just by these big cells, but by these fibers that surround it, and in the center, it's very pale, almost lucent, and these fibers that are staining darkly are fibers going up toward the rest of the brain or coming down toward the spinal cord, and when those fibers are making their way along this route, if there is anything already present, they respect the boundaries of things like facial nucleus.

So they go around it, and we describe that as being a capsule, that the nucleus is surrounded by fibers, okay? If you look at the case with autism, in fact, there is no capsule, and there is no lucent area where the nucleus should have been. Instead -- if I could have the next slide. Instead, what you can see is that those dark staining fibers are just running

willy-nilly through this area.

So that suggests that when they got to this region, instead of going around the nucleus, they just went any which way, because there was no nucleus there, and the facial nucleus forms very early, like the fourth and fifth week of life, and so it would have to have been present when these tracks formed, if it existed, but it didn't.

BY MR. JOHNSON:

Q And Doctor, is this kind of finding consistent with other neuropathological findings reported by other researchers?

A Yes. Dr. Kemper talked yesterday about the case of lack of dying off in the inferior olive, so I'm not going to cover that, but I will tell you another example of something in histology that suggests that autism begins early.

Q Okay, and we are now looking at slide 12?

A Yes. The Purkinje cells are the huge gray cells that you see here, and they have very bright nuclei with a little dot that's their nucleolus. Those are the giant cells of the cerebellum. They are actually so big that you can look at a slide and you can see them with the naked eye. You don't have to put it under the microscope, and those cells are

characterized by being surrounded by axons of neighboring cells, and the black deposit that you see is an immunocytochemical stain for neurofilaments in those axons, and these axons actually form a basket that extends all the way around the Purkinje cell, and you can see them depicted here.

As you might imagine, if one of these cells died at some time shortly before we took this histological sample, it would leave an empty basket, and so pathologists have long looked for empty baskets in cases where the Purkinje cells may have degenerated to find out whether they died recently or whether they were lost earlier, or never formed at all, and in Bailey's study, he tried to find empty baskets and he couldn't find any, suggesting that the Purkinje cells weren't being lost at the present time.

Q Because in his study, are the baskets full?

A The baskets are all full. He couldn't find any empty ones.

Q Meaning that the Purkinje cells had died a long time before?

A Right.

Q Doctor, do some autistic patients have craniofacial dysmorphologies?

A They do, and I have a paper on that that I

mentioned in the report, but many other people have shown this, that the rate of small, minor physical malformations is increased in people with autism.

Q Can you give us some examples? And we are now looking at slide 13.

A Sure. I want you to look at the embryo, and this is a picture of the embryo at 54 days, so that's like in the eighth week post-conception, and I want you to look at the ears. Can you see that the ears are down here on his neck? Okay, that's where the ears form, and then, through differential growth, as the embryo gets older, the ears go from this position and twist so that they are upright, not lying on their sides, but upright, and they move up to the position related to the eye.

And in the next picture, you'll see a typical malformation that's common in autism.

Q And this is slide 14?

A Right, and it's called low-set, posteriorly rotated ears, which describes the condition pretty directly, and these low-set, posteriorly rotated ears obviously did not occur postnatally. In fact, the ears are in place by around the twelfth week. So any problem where you see low-set, posteriorly rotated ears suggests that there was an insult to development

in the embryo.

Q And is there another example of a dysmorphology?

A Yes, I put in a slide of another one, and taking you back to the embryo again, and this time I want you to look at how far apart the eyes are. The human face, and actually other animals' faces, form in such a way that it's as though the face is coming together in the middle. So the middle part is produced first, but then the rest of it comes to join the middle, and what you see in cases of autism, pretty commonly, is that the eyes are too far apart.

So these two little boys both have autism subsequent to exposure to valproic acid, and can you see that their eyes are just a little too far apart? That's called hyperteliorism, and you can see it even more clearly if you look at how far apart their eyebrows are. In fact, they look a little bit more like the embryo I just showed you than like a normal postnatal human.

The fact that their eyes aren't close enough together leaves them with a wide, flat nasal bridge, and makes you wonder whether they could ever wear glasses or not, because their nasal bridge is so wide. These cases are a good example of the fact that

physical malformations, small ones, are not just associated with genetic syndromes. They occur in children like this who have a cause of autism that's environmental.

Q Now, Doctor, you've discussed several factors that lead you to believe that environmental factors, to the extent they play a role in autism, are occurring early in gestation. Now, the issue in this litigation is regressive autism, and I was wondering if you could comment on whether you think that the evidence you've presented is inconsistent with regression in autism.

A No, actually, it's well-known in neuroscience that very early lesions of the nervous system often result in regression.

Q And why is that?

A It is believed to be because, if you look at behavior in very young animals or people -- the big study was done in monkeys -- you can find behaviors that won't occur for some time after birth. So there are tests you can do that you will find that infants do very badly at them, but as their brain matures, they are able to do those tasks. Okay?

So what has been done in the primate literature is to place lesions in these very late-

maturing parts of the nervous system in a neonatal animal, and then, when you compare that animal to a control, they both do poorly at the difficult task. They look just alike, but with the one I am referring to, when the animals get to be about two years old, the controls suddenly are able to do the task with ease, but the lesioned animals not only do not do as well as the normal, control animals, they do worse than they did earlier in life.

That's a regression, okay, and the reason is thought to be that when the animal reaches the age when this very advanced part of the nervous system is supposed to come on line, and you can see that it has in the controls, when they reach that age, apparently, they can't re-access the part of the brain they were using to do the task before. That is, they need to switch to the new system also, but they can't because it's missing. It's been ablated.

So, I mean, people who are familiar with early brain injuries know that regression can follow an early injury.

Q Doctor, based on your knowledge, training and experience, do you believe that the evidence supports the claim that thimerosal-containing vaccines cause or contribute to autistic spectrum disorders?

A I do not.

Q And can you briefly just summarize again the basis for that opinion?

A First of all --

SPECIAL MASTER HASTINGS: Now we are on slide 17.

MR. JOHNSON: Yes, Special Master.

THE WITNESS: I mean, I believe that for many other reasons, but the information I wanted to bring to you is just that there is no similarity between the symptoms of any kind of mercury poisoning and autism, and there's not anything like a similarity between autism and ethylmercury poisoning. And then, it's my belief that the available evidence, both from known risk factors and histology and dysmorphology, indicates that autism arises in the embryo in the first trimester of pregnancy, and there is no evidence that it arises postnatally.

Q And Doctor, do you hold your opinions to a reasonable degree of scientific certainty?

A Yes.

MR. JOHNSON: Thank you. I have no further questions.

SPECIAL MASTER HASTINGS: Thank you, Mr. Johnson. Do Petitioners have questions for this

witness?

MR. POWERS: We will, Special Master. Could we do a quick five-minute break here between direct and cross and then be ready in five minutes?

SPECIAL MASTER HASTINGS: All right, let's take a five-minute break.

MR. POWERS: Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: Please be seated. All right, we are about to go back on the record and Dr. Rodier is in the witness stand. Mr. Powers, go ahead when you are ready with your cross.

MR. POWERS: Thank you, Special Masters.

CROSS-EXAMINATION

MR. POWERS: Good morning, Doctor.

THE WITNESS: Good morning.

BY MR. POWERS:

Q My name is Tom Powers. Along with Mr. Williams here, we represent the Petitioner Steering Committee, as well as William Mead and Jordan King and their individual claims in this proceeding. The initial portion of your presentation today and a significant portion of the report that you filed discussed the 2001 Medical Hypothesis article, correct?

A That's right.

Q And in your direct testimony, you described that article as the reason that we are here today, correct?

A That was the first suggestion anyone has ever -- the first time, to my knowledge, that anyone had ever suggested that thimerosal and autism had a relationship.

Q In preparation for your expert report, did you review the expert reports that were submitted by the Petitioners' experts on general causation in these cases?

A Yes, I did.

Q Did you review Dr. Deth's report?

A Yes. I am not a biochemist, so that one is really out of my area of expertise.

Q Did you review Sander Greenland's report?

A Yes, and again, I am not an epidemiologist, so that one is also out of my area.

Q Did you review Dr. Aposhian's report?

A I did.

Q In none of those reports was the article that you referenced cited or relied on. Is that correct?

A I don't remember whether it was or not. It

wouldn't necessarily have been.

Q And your understanding would be that those materials laid out Petitioners' theory of general causation in these cases, correct?

A Yes, that the expert reports did.

Q Between the time that you filed your expert report and your direct testimony today, did you have a chance to review Dr. Kinsbourne's expert report submitted?

A Yes.

Q Dr. Kinsbourne's report didn't cite the Bernard article that you've been discussing at all, did it?

A I don't think so.

Q None of the general causation reports from Petitioners in these cases cite or discuss the Bernard article, correct?

A I'm not sure, but if you say so, I will agree.

Q Now, in a lot of the work that you've done, it appears that there is an effort to look at minor physical abnormalities and see if there are associations between those MPAs -- is that the right abbreviation?

A Yes.

Q -- between MPAs and autism. Is that a fair statement of a fair amount of your work?

A Some of it.

Q You've also done brain pathology work?

A Uh-huh.

Q In the brain pathology work, how many brains have you actually examined tissue from and generated peer-reviewed published literature?

A Just one.

Q One brain?

(Pause.)

BY MR. POWERS:

Q In the literature that you reviewed that describes the brain pathology work of others, would that involve the same series of studies that Dr. Kemper testified about yesterday?

A Yes. I mean, I've read all of those, yes.

Q Okay, and as he described, those studies involved a total of 23 individual brains, correct?

A Yes.

Q Yes, and I was going to say, the Special Master was about to signal you. When you give an answer, you need to say --

A Yes.

Q -- yes or no. Okay. Because this is being

recorded and we've got to have a good record. So again, the question was, the brain pathology literature that you are relying on is essentially the same series of reports that Dr. Kemper described based on 23 brains?

A Yes.

Q So your work in neuropathology has involved the 23 brains in those studies and the one brain that you looked at, correct?

A Well, my understanding of the neuropathology involves all of those, and I'm sure he was including my case in the 23.

Q I think he was, and he actually did describe some studies that had individual -- that were just single-brain case studies.

A Yes.

Q Now, in those neuropathology studies, there was no correlation made between the neuropathology observed and the particular symptoms that the person from whom that brain was taken presented with, was there?

A I don't recall any very extensive discussion of the symptoms. In the Bailey case, there was probably a little more discussion of each individual case's symptoms, but all of them were ones that met

the criteria at that time for a diagnosis of autism.

Q So it would be fair to say that the neuropathology to date that you've reviewed and that you've relied on cannot correlate neuropathological findings with a specific mix of symptoms in any particular person, correct?

A You certainly can't account for all of the symptoms with the neuropathology, but I think in our report, we certainly had evidence that the things we were seeing in the brain were having effects in the person, for example, that she had poor control of the muscles of facial expression. In fact, she had what is called Moebius syndrome, which is lack of innervation to the face and to the lateral rectus muscle that moves the eye to the side, and we didn't have the tissue to look at her abducens nucleus that moves the eye to the side, but we did have the tissue to see that her facial nucleus didn't contain the normal number of cells.

Q So this one brain and this one particular symptomology, you had a correlation, you believe?

A Uh-huh.

Q In general, the neuropathology has not been able to describe any particular pattern of symptoms that are associated with particular pathologies,

correct?

A In general, but I can tell you one that's from our work that I didn't include in my report.

Q Is this the Brazilian, the Moebius work?

A No. This is the eye blink conditioning that I mentioned yesterday. You know, it has been shown in many of the neuropathology studies that the number of Purkinje cells in the cerebellum are reduced, and in eye blink conditioning, we know that the Purkinje cells provide the control of the timing of the eye blink response, and the size of it, and in people with autism, they blink a little too early and they blink harder than most people.

And so that shows there is something amiss with the Purkinje cells.

Q Now, eye blinking rate and strength of eye blinking, is that part of the diagnostic criteria for autism?

A No.

Q In terms of the diagnostic criteria for autism across the three domains, did any of your work show that there is a correlation between the neuropathology and particular presentation of language skills in individuals with autism?

A No.

Q Any work that associates particular neuropathologies with the presentation of behavioral skills in particular individuals with autism?

A I'm not sure what you mean by behavioral skills.

Q We are talking about the behavioral skills that are one of the domains that are assessed in diagnosing autism.

A Do you mean social behavioral skills or communicative behavioral skills?

Q More the play and behavioral skills.

A Okay, that's considered a social skill.

Q And there is no correlation between the neuropathology and any collection of symptoms in any individual with autism?

A No, because none of the symptoms that are used in diagnosis are associated with any particular region of the brain. No one knows what part of the brain controls peer relationships or imaginative play.

Q No correlation between the timing of onset of symptoms and any particular manifestations of the neuropathology, correct?

A If I understand your question, and I'm not sure I do, Dr. Kemper said yesterday and I have said today that there are many things in the pathology that

suggest a very early origin of the injury.

Q But there is nothing that associates specific symptoms that would be diagnosed in any individual with the neuropathological findings? You are saying it suggests an early onset, but my question is, does any of the neuropathology correlate with specific patterns of symptoms of people diagnosed with autism?

A I would say no.

Q And that would be reflected in the DSM-IV criteria, correct, where there is -- we talked about this with Dr. Kemper and you were here yesterday -- where no specific pattern has been identified correlating any neuropathological issues with the presentation of symptoms, correct?

A Not with the diagnostic symptoms, right.

Q You talked about neural lesions. In what percentage of human beings who have been diagnosed with regressive autism is there evidence of neural lesions in their brains?

A No one to the best of my knowledge has done any pathological work where they took cases who were regressive and compared them to others.

Q So the answer would be no, there's no instance of a person with regressive autism who has

been found to have a neural lesion?

A No.

Q You talked about environmental factors that may contribute to autism. You had it in your report and you described it on direct testimony. Do you have your report in front of you?

A I do.

Q I am going to ask you to turn to page 4 of the report.

A Okay.

Q Okay. There is subheading B and it says, the known environmental risk factors for autism all act in the first trimester of pregnancy. When you say 'known environmental risk factor,' what are you referring to? As you describe it here, what attributes of a risk factor are there in order for it to be known, as you describe?

A That it's been demonstrated in an epidemiological study, a population study.

Q So your description of risk factors here is limited to risk factors that have been examined in population studies, in ecological studies?

A Not ecological studies, but population studies.

Q Population studies? So are you excluding

case series and case studies from your description of environmental risk factors here?

A I'm not, actually, I'm not aware of any of those in -- that speak to the issue of environmental factors.

Q Are you familiar with any case reports or case studies that associate malaria in young children with the later presentation of autistic symptoms?

A Actually, I have seen some of those.

Q Are you familiar with studies that describe the possible implication of other viruses, such as Borna virus, in the later development of autism postnatally in children?

A I am not familiar with that one.

Q Are you aware of any case studies that describe encephalopathies, acute encephalopathies postnatally, that are then associated with the later development of autistic symptoms?

A With the subsequent development of autistic symptoms.

Q Correct.

A There are a few of those cases in the literature, but I believe that they are examples like the example I gave you of tuberous sclerosis, where if you injure the brain enough, you will eventually

produce some of the symptoms of autism.

Q Right, and these are cases that do describe postnatal injuries or events that produce autism, correct?

A With very, very severe brain damage.

Q As I take it from looking at your work, one of the theories that you have advanced is that there are the possible involvement of the hindbrain or the brainstem in early development and the later development of autism, is that correct?

A That's correct.

Q And in examining that hypothesis that fetal hindbrain or brainstem development might be associated with later autistic symptoms, you looked up potential genetic contributions to that etiology, is that correct?

A Yes, and many of the genes that have been proposed as candidate genes for autism susceptibility are early developmental genes involved in the formation of the brainstem.

Q Right, and my understanding is that a number of years ago, you published a paper that examined a particular genetic location, the homeobox A1?

A That's right.

Q It's a particular location on chromosome 7,

is that correct?

A Yes.

Q And that particular coding section codes the proteins that help guide the early alignment and development of, is it the hindbrain or the brainstem?

A It's the brainstem.

Q So you published on that, and one of the hypotheses there was that variations in the -- is it H-O-X A1? Is that the easiest way to --

A Hox-A1.

Q Hox-A1. Thank you. The more that I can use abbreviations scientifically, the more I appreciate it. So the Hox-A1 coding site on chromosome 7, the hypothesis was that anomalies there might be associated with autism down the road, correct?

A Right.

Q And there was a series of papers that were published after your article that addressed that question, correct?

A Yes.

Q And in 2002, Professor Lee's article came out, and that article held that it's unlikely that the Hox-A1 findings play a significant role in a genetic predisposition to autism, correct?

A That's right.

Q There was another article that came out, also in 2002, with a larger study, and that study concluded that, even though the study had enough power that they were 95% confident they could identify even a 1% contribution of Hox-A1, they concluded that the evidence didn't support an association, correct?

A That's right, and these are papers on the same polymorphism in Hox-A1 that we had examined.

Q Right. And then in 2004, a third paper came out saying that the Hox-A1 gene is unlikely to be a susceptibility gene for autism, correct?

A Uh-huh. And then in 2005, a group of patients were studied in Saudi Arabia and Turkey who had a larger polymorphism or mutation in Hox-A1, and it turned out that they did have autism.

Q And in all of these studies, it hasn't been described as causing autism, but as a genetic susceptibility or a genetic vulnerability to autism?

A That's right.

Q There was a study that you did -- where is it -- is it Nova Scotia?

A Yes.

Q Okay, and this is Respondent's Exhibit No. 401, and it's going to be on your screen in just a moment.

A Okay.

Q Okay, take a look at that screen, and does that -- oh, I'll just ask you. What does that appear to be on your screen?

A That's our paper from *Teratology* in 1997, I think it was.

Q Okay. Now, what I would like to do is turn to the -- and again, this is Respondent's Master List 401. We're going to turn to page 3 of the exhibit, and Doctor, for ease of your reference, the text page in the report is 321, and there is a table there. I wanted to zoom in for a second on Table 2.

A Okay.

Q And that very first category there where it says 'ear rotation'?

A Uh-huh.

Q Is that the ear dysmorphology that you were describing in your slide presentation?

A Yes, it is.

Q Okay, and you've found that in this population of children in Nova Scotia, that 42% of the autistic children had the ear rotation that you described, correct?

A Yes.

Q Now, 18% of the controls also had that,

true?

A That's right.

Q So is it your hypothesis that whatever genetic coding going on in early development that produced the ear rotation malformation also produced autism?

A I think that -- could you rephrase that question?

Q Is it your theory that the same genetic coding that directed the ear rotation resulting in this malformation also caused autism?

A We don't know whether it was genetic or not. I showed you that these malformations can also be caused by environmental factors, so we don't know whether these were genetically caused or not, but we think that they are related, that the timing, since there is evidence that something went wrong in development, that it's most likely that that's when the autism started.

Q Now, the 18% of the controls that had this identical -- it's called a malformation, just the different degrees of ear rotation. 18% of the controls had that. Now, they did not have autism.

A That's right.

Q So there's something that happened

differently with the controls than with the autistic children, even though they had the same dysmorphology, and they had very different outcomes, correct?

A Yes.

Q So at best, any of the early developmental processes that generate these malformations would indicate not that that process caused the autism, but that it was a susceptibility or vulnerability to the later development of autism, correct?

A I think it speaks more to the issue of there being some event early on that seems to be related to the autism.

Q And some event early on that, at least given the evidence that controls who experienced the same event don't develop the symptoms, at least leaves open the possibility that something that happened later affected the ultimate presentation of symptoms in the children that were autistic, correct?

A Yes, that's possible.

Q Okay.

A But in science, we strive for parsimony, and if you already know that there was an event that did something to disturb development, you don't propose that there was probably a second event, unless there is evidence for it.

Q Now, would you disagree -- and we're done with the paper here. Would you disagree with anybody who presented at the Institute of Medicine meeting in April of 2007 that looked at the issue of potential environmental contributions in the etiology of autism, do you disagree that there may be environmental factors that come into play in autism?

A No.

Q You don't disagree?

A No.

Q Would you agree that it is possible and biologically plausible that in some cases, there could be postnatal environmental factors that might result in the appearance of autistic symptoms?

A It's a very outside possibility that a very late injury, unless it's, you know, overwhelming brain injury like with an encephalopathy, that a very late injury would give you the same behavioral effects that you see after early injuries.

Q Would you disagree then with the recommendation that NIH -- at least the person who was, Dr. Insel, who was presenting -- that NIH ought to be devoting research money into postnatal environmental contributions to the development of autistic symptoms? Do you think that that's a waste

of money?

A I certainly wouldn't say that no one should try to study it, but given how successful it's been so far, I would doubt that it would be very successful in the future.

Q Any of the work that you've done in looking at dysmorphology -- oh, actually, a question also on the dysmorphic issue. What percentage of children with regressive autism have dysmorphic physical features?

A I am not aware that anyone has ever looked at the -- has reported physical dysmorphologies in regressive versus non-regressive cases.

Q Among cases that are non-regressive, what percentage of non-regressive cases of autism have identified dysmorphologies associated with them?

A I think it depends on who is looking for the dysmorphologies and which ones they are looking for, but I know in our sample, we have run around 50% have dysmorphic features of some sort, and in the cases in Rome collected by Tony Persico, he says 52% in his sample.

Q So it sounds like about half, correct?

A Yes.

Q So, and those are specifically in the non-

regressive cases, but again, in the regressive cases of autism, you are not aware of any data that even associates the appearance of physical dysmorphologies with the symptoms of regressive autism, correct?

A No, I am not, but both Persico's series and ours would have included some cases of regressive autism.

Q Do you know that?

SPECIAL MASTER HASTINGS: Let me interrupt. That's the point I wanted to make to your previous question, Mr. Powers. You ask her -- she said there was no difference between regressive and non -- she didn't know that anyone had looked at regressive versus non-regressive, and then you asked her, well, in the cases of non-regressive, and you said, Dr. Rodier said about 50%, but when you answered that --

THE WITNESS: No, he said that that was in non --

SPECIAL MASTER HASTINGS: I'm sorry?

THE WITNESS: He said that that was in non-regressive. I didn't say that.

SPECIAL MASTER HASTINGS: Well, actually, in the question before you answered, I think he mentioned it too, and I didn't think you picked up on that, so I want to make sure I understand. When you were talking

about the studies that have found about 50 or 52%, those studies made no distinction between regressive or non-regressive, correct?

THE WITNESS: That's correct.

SPECIAL MASTER HASTINGS: All right. I just wanted to clarify that.

BY MR. POWERS:

Q So they made no distinction, and so the issue is that an association of physical dysmorphologies with regressive autism is an inquiry that has yet to have been made. Is that a fair statement?

A That's right.

MR. POWERS: Thanks. No further questions.

SPECIAL MASTER HASTINGS: Go ahead.

MR. JOHNSON: I have just a couple.

REDIRECT EXAMINATION

BY MR. JOHNSON:

Q Doctor, you were asked some questions about your own brain studies, and you were asked how many you had studied and you answered one. Based on your study of that brain, did your findings make sense biologically? In other words, did the things that you found match up with what is kind of scientifically understood about biology and development?

A Yes.

Q So even though your data is limited, it is consistent with other established scientific data?

A Yes, and I should say, I think this is an important point. The different studies, the different histological studies that have been done all have their strengths and weaknesses. We had just one case, but we did serial sections of that case. That is, we had just part of a brain, and so it wasn't that expensive to do thin serial sections of the whole length of the tissue that we had.

In most studies of larger case series, in Dr. Kemper's set, their sections are incredibly thick, so they have difficulty studying small nuclei, whereas we could study that. In Bailey's case, they couldn't afford to take sections except every couple of millimeters, so they didn't even have a chance to hit most of the small nuclei that are smaller than a couple of millimeters.

So those studies are good because they have multiple cases, but they are bad because there are a lot of parts of the brain they couldn't study.

Q But in general, is the study of these brain sections, is it fairly painstaking?

A Yes.

Q Okay.

A Especially if you are doing cell counts.

Q Okay, and in the studies that have been done, are the findings generally consistent between the brains that have been studied?

A Some of the things are fairly consistent, especially the low number of Purkinje cells, but there are other things that one person has reported and no one else has reported. But this is a very slow process. I will give you an example. One of the things we found in the brain that we studied was a complete absence of a part of the superior olive, which is an auditory relay nucleus, and it's the first one where information from both ears comes together in the nervous system, and so it's important in sound localization, okay?

And we reported that. It was very striking in our brain. No one else has ever reported it. No one else has said that the superior olive was normal. They just didn't look, and just two months ago, a group of people who actually studied a superior olive got hold of the superior olive from one of the brain banks for five cases, and in fact, all five of them were abnormal.

So that's an example of something that was

reported in 1996. No one else saw it until 2008.

Q Doctor, you were also asked some questions about the environmental risk factors that you identified and why you selected the ones that you selected, and I just wanted to be clear. Did you select the ones that you presented today because there is good epidemiological data on those?

A Yes.

Q Okay, and so you weren't considering case reports and case studies because those don't really provide good evidence of a causal association?

A No.

Q And Doctor, I just want to ask you, as a scientist who studies human development, what is more likely, that the early problems in prenatal development cause problems later in development, or that a postnatal exposure causes autistic regression?

A Early injuries produce a cascade of further injuries in the nervous system, and this has been shown, so I would favor the idea that early injuries are the most likely to be involved.

MR. JOHNSON: Thank you. That's all.

SPECIAL MASTER HASTINGS: Mr. Powers, anything further?

MR. POWERS: We have no further questions,

Special Master.

SPECIAL MASTER HASTINGS: Special Masters?

SPECIAL MASTER VOWELL: I have a question, well, probably several for you, Dr. Rodier, and my questions deal with the follow-up on some of Mr. Powers's questions. That is, we have heard testimony or read reports that involve people with postnatal exposures to certain viruses or other factors who develop autistic-like symptoms. Herpes encephalitis, for example.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Given your testimony that the onset of the injury occurred probably in early prenatal development, how do you square that with evidence that something postnatally can cause very similar symptoms?

THE WITNESS: I think that in those rare cases, like the malaria cases, the herpes encephalitis cases, that what you get is tremendous brain damage, and it probably includes many symptoms besides the symptoms of autism, but if you damage the brain enough, you'll eventually damage the parts involved in autistic behavior, although it actually won't be, technically wouldn't meet the present criteria for autism unless it occurred before age 3.

SPECIAL MASTER VOWELL: Age 3, right. So you are saying that a postnatal insult that involves incredible brain damage can mimic the symptoms, although having a very different cause from what you see in terms of classically diagnosed autism?

THE WITNESS: Right, and you know, I am making that distinction because I think the thing that is fascinating to scientists is that the symptoms of autism can occur in someone who has no other symptoms at all. We have a case in Rochester who has an IQ of 150, but has frank autism, so many cases of autism don't look like they have overwhelming brain damage, but they have something, some alteration in their development that interferes with very specific kinds of behaviors, and I think that people who work in autism, you know, that's the thing that they are trying to understand.

SPECIAL MASTER VOWELL: I think in analogies, so let me give you this. Let's say that a child suffers a prenatal insult that takes away the ability to see. Does that happen?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay. Then a child suffers some sort of brain inflammation or brain injury that takes away the ability to see. Those are

similar symptoms with very different causes.

THE WITNESS: Right.

SPECIAL MASTER VOWELL: I understand what you are --

THE WITNESS: What I am struggling to get at.

THE WITNESS: Yes, I understand the case that you've described of -- vision can be lost at any age, okay. What's different in a condition like autism is, from the vision analogy, is that most people think a big part of the problem in autism is that the connectivity of the brain is not right, and you know, you probably heard other people say that and you'll hear Casanova say that, that the connections that are formed aren't right.

It's not that they have big holes in their brains, you know. It's, for some reason, the connections didn't form properly, and that process, that basic process, is going on like crazy in the embryo, okay, and in the first few months in utero. By the middle of gestation, things like cell migration are complete, and now the final stages of making connections can occur.

There are connections being made probably throughout life but the basic ones are set up, you

know, the basic tracks, the basic pathways, the connections between the two sides of the brain and the forebrain with the hindbrain, etc., those pathways are all present soon after birth, so that a disruption, to disrupt those pathways would have to occur early, and what I have trouble imagining, just from picturing the development, that long series of events, is that you could then go in later with some kind of global injury that would give you exactly the same misconnected brain that you can produce early.

SPECIAL MASTER VOWELL: So, if you took my two children, the one with the prenatal injury and the one with the postnatal, after-birth injury, and you looked at their brains, even though the symptom is the same, neither of them can see, the mechanism, what you would see in their brains would be very different?

THE WITNESS: Well, they wouldn't necessarily have brain problems. They wouldn't necessarily be blind because there is something wrong with the brain.

SPECIAL MASTER VOWELL: Well, maybe I'll come up with another example that is something wrong with the brain. Ataxia, perhaps? What I am trying to get at, and obviously doing it inarticulately, is, do we see similar symptoms with different brain

neurophysiology? That is, you've described to us what happens, the missing baskets, the absent Purkinje cells. Can you get similar symptoms with a postnatal insult that do not necessarily involve those findings?

THE WITNESS: I don't think we know the answer to that.

SPECIAL MASTER VOWELL: Okay.

THE WITNESS: I think it depends, it would depend on whether the behaviors you are looking at are ones that the underlying problem is one of connectivity or just one of pure structure.

SPECIAL MASTER VOWELL: Absence.

THE WITNESS: I mean, for example, you could be blind because the retina failed to develop. You could be blind because the occipital cortex failed to develop. You could also be blind because somebody hit you on the back of the head and damaged your occipital cortex, and those would have the same -- could have the same symptoms, but through different kinds of mechanisms.

SPECIAL MASTER VOWELL: And so histopathologically, if you looked at the brain, you would see different, there would be different findings?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay. That was what I was trying to get at, that this is not the only explanation for autistic symptoms, this early -- and I am talking about autistic symptoms, not a diagnosis of autism.

THE WITNESS: Right. Yes, that's right.

SPECIAL MASTER VOWELL: So you could develop autistic symptoms postnatally without having the same histopathologic findings in the brain that you've described, through other mechanisms than those you've described?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay. Those are my questions.

SPECIAL MASTER HASTINGS: Any questions?

SPECIAL MASTER CAMPBELL-SMITH: No.

SPECIAL MASTER HASTINGS: Any further questions based on Special Master Vowell's questions?

MR. POWERS: Not from the Petitioners. Thank you.

MR. JOHNSON: Nothing from Respondent.

SPECIAL MASTER HASTINGS: All right, then, Dr. Rodier, we thank you very much for your testimony.

THE WITNESS: Thank you.

SPECIAL MASTER HASTINGS: You are excused at

this point.

(Witness excused.)

SPECIAL MASTER HASTINGS: Is Respondent ready to call the next witness, then, at this point?

MR. MATANOSKI: Yes, sir.

SPECIAL MASTER HASTINGS: Do we need a break, or?

MR. MATANOSKI: Could we have a brief break just to get set up, sir?

SPECIAL MASTER HASTINGS: Okay, how long do you need?

MR. MATANOSKI: Five minutes, sir.

SPECIAL MASTER HASTINGS: Five minutes? Okay, we're going to take a five-minute recess.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: Please be seated, folks. We are ready to proceed with the next witness, I believe. Dr. Goodman is seated at the witness table, and Ms. Ricciardella, when you are ready, please proceed.

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER HASTINGS: Oh, actually, I should swear the witness.

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Whereupon,

STEVEN GOODMAN

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

SPECIAL MASTER HASTINGS: Please go ahead, Ms. Ricciardella.

MS. RICCIARDELLA: Thank you.

DIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Good morning, Dr. Goodman. Could you please state your name for the record?

A Steven Goodman.

Q And what is your current position?

A I'm a professor of oncology, epidemiology, biostatistics and pediatrics at the Johns Hopkins School of Medicine.

Q And would you briefly review your educational background post-high school?

A Post-high school? Okay. Going back a long way. I got a B.A. from Harvard where I studied applied math and biochemistry. I got then an M.D. from New York University, and then trained in pediatrics at Washington University at St. Louis, was board certified, then got a master's degree in biostatistics and a Ph.D. in epidemiology from the

Johns Hopkins School of Public Health.

Q And are you a medical doctor?

A Yes.

Q And are you board certified?

A Yes.

Q In what?

A In pediatrics.

Q Okay, and what licenses do you hold?

A I no longer hold an active license. I held a licensed practice until the late 90s when I surrendered to epidemiology as my real profession.

Q And would you briefly describe your academic employment history?

A I have been on the faculty of the Johns Hopkins School of Medicine in the Department of Oncology, with joint appointments in epidemiology and biostatistics since 1989.

Q And in what professional societies are you most involved?

A The one where I am most involved is something called the Society for Clinical Trials, where I serve on their executive board. I am currently editor of their journal, and I am also a member of the American Statistical Association and International Biometric Society, and have been a

member of a variety of epidemiologic organizations.

Q Now, your CV states that you are on various advisory committees. Could you explain what your role is in those advisory committees?

A Yes, I am on several. I serve as a scientific advisor to what is called the technology assessment program of the National Blue Cross/Blue Shield Association. This is an expert panel of leading scientists and physicians from around the country that looks at new medical procedures, interventions, and tries to decide from emerging evidence whether there is enough evidence to conclude that it works, basically.

I served in a similar capacity on the Medicare Coverage Advisory Commission, where they do exactly the same thing. They look at emerging evidence of the efficacy of medical procedures and interventions to decide whether they are likely to work and whether Medicare should cover them. Let's see, the others. Those are the main ones at present.

Q And do you hold any teaching positions in your specialty?

A Yes. I teach a number of courses in the Department of Epidemiology at Johns Hopkins. I teach a three-term doctoral seminar that's required of all

doctoral students on basic principles, not just basic, advanced principles of epidemiology and issues in inference. I teach a course in meta-analysis, systematic reviews or evidence synthesis, taught that for ten years.

I teach a course in clinical research methods, both during the regular term and I also teach that during the summer, and I also lecture in a number of other courses on ethics of clinical research.

Q Now, are you a full professor?

A Yes.

Q And you mentioned that you give lectures. Do you also give lectures to professional groups and organizations?

A Yes.

Q What topics, usually?

A They are usually on the issues of inference and evidence synthesis, that is, how to draw conclusions from data.

Q And to whom would you give such a lecture?

A I have been invited to many groups, the FDA, CMS, I have been invited to talks of various epidemiologic societies.

Q And what is CMS?

A I'm sorry. That's Medicare, the Center for

Medicare and Medicaid Services. Groups like this. Training sessions for staff who have to synthesize the evidence.

Q And do you lecture internationally as well?

A Yes, I do.

Q Are you actively involved in research?

A Yes, I am.

Q Could you explain in what ways?

A Well, I have been a member of and now director of a division of biostatistics in our Department of Oncology, and the main role I and fellow faculty there have is to collaborate with other researchers, both in the Cancer Center, but also throughout the medical school, in virtually everything that they study. So we do everything from very basic laboratory research -- that is, we don't do it, we work with the scientists who do it -- to large-scale epidemiologic studies, and that's where I spend my time when I'm not teaching.

Q And is epidemiology itself a science?

A Yes, it certainly is.

Q And you've published over a hundred scientific articles? Is that accurate?

A Yes.

Q And are they all peer-reviewed?

A Yes.

Q And what have been the primary subject areas of your publications, if you could distill it to a few subject areas?

A Well, the primary areas of the collaborative research is cancer, although I have published articles on many other disease areas as well. My own work tends to be in areas of inference, and how to, again, methods and principles underlying how to draw conclusions from usually uncertain data. I have also actually done research on peer review, believe it or not. I think that was peer-reviewed too, and those are the main areas.

Q And in addition, you've authored six book chapters, is that correct?

A Yes, that's true.

Q And your CV states that you wrote the lead chapter in the 2004 Surgeon General's Report on Smoking, is that right?

A Yes.

Q And what did that entail?

A That was the chapter that laid out the principles and categories of conclusions that were to be used in the causality assessments in the subsequent chapters, which all focused on links with specific

diseases to smoking, but this set out the framework and the principles by which each of the contributing authors would use to make that assessment.

Q And do you have an editorial role in any medical journals?

A Yes, I have been the senior statistical editor for the *Annals of Internal Medicine*, which is one of the world's leading medical journals, since 1987. I am also editor-in-chief of a journal called *Clinical Trials* that I mentioned before, which focuses quite generally on clinical research methodology.

Q And are you a reviewer for any journals?

A Yes, I am a reviewer for many journals. I was associate editor for another journal, the *Journal of General Internal Medicine*, for several years.

Q And Dr. Goodman, have you testified in a court of law before?

A Yes, I have.

Q How many times?

A Twice.

Q And could you describe what those cases were about?

A One was a malpractice case in Florida. It had to do with a misdiagnosis, and I was called down there as someone who could comment on the evidence

underlying the prognostic -- the likely fate of the patient had they not had the delayed diagnosis. It involved looking at the literature. In the other case, it was the Fen-Phen case. It was a tort case where I was brought into it after the settlement had been reached -- people in the courtroom will know the language better than I -- to advise on the fairness and whether the settlement that had been reached was equitable and fair or based in science, so I was given the underlying data they had to reach the settlement and the compensation grid, and I advised the court on whether that was reasonably based on the underlying evidence.

Q Have you ever testified in relation to epidemiology and autism?

A No, I have not.

Q Now, Doctor, your CV states that you have been a member of various committees of the Institute of Medicine, is that correct?

A Yes.

Q What is the Institute of Medicine?

A The Institute of Medicine is an independent body that I believe is chartered by Congress. It's a branch of the National Academy of Sciences, which was originally started in the mid-1800s. The Institute of

Medicine as an independent entity within that was started I think about 1970, and it's a body that is specifically tasked with providing independent, objective, expert scientific advise to Congress and to federal agencies and other official bodies within the U.S. government, but it's completely independent of them.

Q And how is the Institute of Medicine regarded in the scientific community?

A I would say -- it's hard to speak for the entire scientific community, but I would say it's one of the most highly regarded bodies, both election to the Institute of Medicine, which is separate from serving on the committees, is one of the highest honors that a scientist, an academic scientist or practicing scientist, could achieve, and their work is generally very highly regarded, mainly by dint of the quality of the products that it's produced over the years, and the quality of the people who work on them.

Q Do you know how IOM -- I'm going to use the acronym IOM -- IOM committees are formed?

A Well, I've not been on the side of choosing the committees, but since I've been on a few, I have some insight. The IOM staff, which includes the leadership, possibly members of the Academy, and staff

who worked on a topic, try to find people who they regard as expert or have relevant expertise in a particular area related to the report that they are constructing in panel.

They usually have a number of domains of expertise that they try to cover, and they -- I assume they look through the literature, they look through talking to other scientists and try to find people who they think are both of high reputation and highly respected to be able to opine on the various subjects that they address.

Q So committee members are selected by the IOM?

A Yes, they are.

Q And what is the role of a committee member?

A I think that varies by committee. On the committees that I have been, our role has been to read through all the evidence in the form of published reports. We also listen to public testimony and evidence that's presented to us in public session, and it's our job to both come up with the conclusions and drafting of critical language that's in the report. Much of the bulk of the body of the report is written by staff, particularly things like evidence tables, but all of the key -- but this is guided by the

deliberations of the panel, and all of the language is reviewed by all the members of the panel before it's finalized.

Q That brings me to my next question. Would you briefly discuss the peer review process at the IOM?

A Yes. Again, I know this indirectly, but first of all, the reports go through many rounds of revision before it's sent out for peer review. Once it's sent out for peer review, they identify a panel of scientists. It can be as many as 10 or 15 or 20, and that report is sent to them. They send comments back, and the whole process is brokered by a review manager, who is, again, a hugely respected academic.

It doesn't necessarily have to be a person who is an expert in that specific area, but they are an expert in being a fair judge of whether the panel adequately responds to the reviewers' comments. So the panel does not have to agree or change their conclusions on the basis of the review, but they have to offer good reasons for every change they do or do not make. They have to respond to every single comment that's made, and those reviewers are not known to us at the time of the review, nor is the review manager.

We have no idea where they are coming from, but ultimately, their names are published in the book. That's actually the first time, in the report, that's the first time we ever know who read the report. And the other thing I will say is, after that comes back to the IOM, it then goes through several further levels of review up through the leadership, up to the president of the Institute of Medicine, and it's only when it passes that level that the report is issued.

Q Now, your CV states that you were on the IOM Immunization Safety Review Committee. Is that correct?

A That's correct.

Q Doctor, do you know why that committee was formed?

A I think it was formed because of concern by both Congress and also the CDC about a variety of hypotheses that were being proposed, and it was felt that it was extraordinarily important that the evidence underlying these hypotheses by adjudicated or judged in a fair and unbiased fashion, both for the purposes of science and public health and also because of the concerns of the public. Just that.

Q And when was it formed?

A This committee, well, we first met in 2001.

I think obviously the process of formation preceded that by about a year.

Q And how many members served on the committee?

A Thirteen, I believe.

Q Okay, and how many medical institutions were represented on the committee?

A I'll have to go back. I think it was 13. It might have been 12.

Q Okay. From across the country?

A Yes.

Q And in 2001 when the IOM first met, what outcomes were they looking at? Clinical outcomes.

A Right. Well, you could just look at the sequence of reports. We had a whole series of reports. The very first one was MMR and autism, that is measles-mumps-rubella vaccine, and autism specifically. And the second one was on thimerosal and -- I believe it's the second one -- and developmental disorders. Then there was a whole range. There was also polio vaccine, SV40 and cancer, related to a contamination of polio vaccine, and there was a series of eight reports which, the final one was re-looking at the MMR hypothesis and autism, and the thimerosal hypothesis, although this time it was

specifically on autism. The previous report was on more unspecified developmental problems.

Q Now, getting back to the membership of the Immunization Safety Review Committee, do you recall what the specialties were of the individual members, generally?

A They were, having recently reviewed it, we had a neurologist, pediatric neurologist, a neonatologist, immunologist, epidemiologist, biostatisticians, folks who were expert in issues of risk communication, public health, vaccine biology, and I think that may cover the territory.

Q There was no toxicologist on the committee, is that correct?

A No, there was not. When I reviewed it, I saw that there wasn't on this committee. I believe there were toxicologists who may have been among the reviewers, but we didn't have anybody specifically expert in that area.

Q In your opinion, the fact that there was no toxicologist in the committee, did that affect the IOM's conclusion?

A No, I don't think it would have affected our conclusions at all.

Q Now, you've been a member of other IOM

committees as well, correct?

A Yes.

Q Could you just briefly state a couple of those?

A The first one was Agent Orange and health outcomes in veterans. The one following my service on the immunization safety was the treatment of PTSD in veterans, which is --

Q Post-traumatic stress disorder?

A Yes, which is a big issue these days, as we know.

Q I would like to turn the discussion briefly to the 2001 report that the Immunization Safety Committee issued. What conclusions did the 2001 committee make with regard to the hypothesis of thimerosal-containing vaccines causing autism?

A That conclusion was that the evidence was inadequate, basically, to make a judgment on that, and it was on developmental disorders --

Q Correct. I misspoke.

A -- generally. The reason they said that was that there were at that time no epidemiologic studies that addressed the question, and that the biologic studies underlying the hypothesis were, as described at the time, fragmentary.

Q And did the committee recommend that additional studies be done?

A Yes, and in fact, they were done.

Q Now, in 2001, the committee used the phrase 'biologically plausible,' but I note that in the 2004 report, they changed their phrasing. Could you explain why?

A Yes. The phrase 'biologic plausibility' was used, I think, in a somewhat informal and unfortunate way the first time, and it's explained in detail in the last report why it was changed.

Q You mean the 2004 report?

A Yes, the 2004 thimerosal autism report, or vaccines and autism. It was originally used in the sense of just saying that this is possible. It doesn't violate physical principles. That is, we knew that mercury is a neurotoxin. There is no question that it's a neurotoxin. So the idea that it could produce some form of neurologic disease was not impossible, not at all impossible.

So it was used in this sort of technical sense that, as opposed to biologically implausible, that is, or biologically impossible, that it didn't violate any known biologic or physical principles or rules, and that was the only sense in which it was

used. It then became apparent to the committee when the report was received that this phrase was inappropriately vague and nonspecific, and that it was taken by many to be -- it was interpreted by many as saying that the hypothesis was likely or probable, which was in no way the sense that it was used.

So the committee decided in later reports, actually decided even in the next report, to be much more precise about how it was evaluating the biologic evidence, and it lays this out in the 2004 report. First of all, they refer specifically to biologic mechanism, and then they divide it into three categories. They divide the description of the biologic mechanism into it being theoretical only, and this might be the realm in which 'biologically plausible' could fall.

'Theoretical' would be an explanation that could be true, that hasn't been demonstrated in any experimental settings, but it's not impossible and could rise to the level of, now we should test it. So that would be theoretical. You wouldn't deem something theoretical if it was completely a crackpot theory. So it had to at least rise to some minimal level of credibility to be theoretical, but it would still be theoretical. It would be just something that

was posed as a possibility worthy of exploration.

Then there was 'experimental,' which is maybe pieces of the mechanism had been demonstrated but by no stretch of the imagination had the entire mechanism been demonstrated, and so we could judge something as experimental if there was enough of the causal pathway there shown in the laboratory or in other clinical experiments, and we would rate that then as weak or strong.

And then finally there was, I think it was 'proven' or 'demonstrated,' that you actually could show in a human being that such and such an exposure caused this outcome with virtual certainty, and an example of that was Guillain-Barré syndrome shown in a person who was re-challenged with the same exposure, the same vaccine, and continually would get it. So those are the possibilities of mechanistic categorizations.

So we were much more explicit in all subsequent rounds to make sure that the public would understand the distinction between biologic hypotheses which were speculative, worthy of pursuit, versus mechanisms that were empirically shown and accepted.

Q Now, the committee met again in 2004, is that correct?

A Yes, that's right.

Q Why was it convened again?

A Well, the main reason, aside from continuing concern over these particular hypotheses, that is both the MMR and the thimerosal-autism hypothesis, one of the main reasons was that there was now a moderate amount of epidemiologic evidence that had come in since 2001. So it was felt that this subject deserved further attention. There was now more evidence, or I should say, evidence, to consider, and they wanted us to weigh in on that.

We, by the way, the panel itself did not decide what topics we were to address. This was decided at higher levels, and we were told that this is what you will be studying, you know, this six months.

Q And what was the clinical outcome that was specifically studied by the 2004 committee?

A Autism.

Q And by autism, do you mean autism spectrum disorders?

A Yes, both. Both that and autistic disorder.

Q And what were the types of evidence that were presented to the 2004 committee?

A I think we saw quite a range of evidence.

We saw the epidemiologic evidence. We were also presented with an array of laboratory animal clinical-type studies that related to the hypothesis.

Q Was the public invited to comment as well?

A Yes, we had public session.

Q Did you have letters presented as well?

A Yes, we did.

Q Okay. Now, Doctor, what were the possible causal conclusions that were available to the committee in 2004?

A Those were: a causal connection is proven; the evidence favors a causal conclusion -- I should actually look and see. Well, this will come very, very close. It favors a causal conclusion; the evidence is inadequate, meaning it's too weak or conflicting or sparse to make a conclusion -- oh, I left out one, that there is no evidence. So that's a possible conclusion, there is simply no evidence. So that's separate from inadequate evidence.

So, no evidence, establishes a causal conclusion, favors a causal conclusion, inadequate for a causal conclusion, and favors rejection of a causal relationship.

Q And what's the conclusion that the committee reached in 2004?

A It concluded that it favored rejection of this hypothesis.

Q Was that a unanimous decision among all the committee members?

A Yes, it was.

Q And when is this 'favors rejection' category typically utilized?

A It's used, well, this is a signal case. It's used when all the evidence points away from a causal relationship and there is no countervailing biologic or mechanistic evidence that in any way would contravene that evidence. I have to be very, very clear, and it was stated very clearly in the report. It absolutely doesn't mean that it absolutely rules out the possibility of a relationship.

That's actually almost literally impossible to do unless you show that something is physically impossible, and we will talk more about the nature of epidemiology and epidemiologic results and why it makes it very difficult. So it's really just a verdict or a conclusion that says the weight of the evidence is on one side and points away from a conclusion.

I would say that we felt it was very, very important to say that, because we felt that we were

speaking to the public as well as to the public health agencies, but there were many, many very, very concerned parents who were facing vaccination of their children at that time. Actually, I was. I had a child who was exactly that age and exactly when we were doing this report I had to decide on vaccination, and there were parents who had children who were autistic, for whom conclusions like this could have a tremendous emotional impact, because they had their child vaccinated.

So we were aware that we had to speak to what we think the evidence really pointed to, because there were real high stakes for the parents as well as the public health community, and we couldn't get caught up too much in technical quibbles when the evidence pointed in one direction or the other.

Q Do IOM committees frequently come to that conclusion?

A No, they generally don't. They did a few times in the Agent Orange arena, but usually the conclusions range from inadequate to favors acceptance. They usually don't come out and say favors rejection, but I have not done a census of all the reports.

Q Now, Doctor, it's been said that the IOM

committee recommended that no additional resources be used to explore a causal relationship between thimerosal-containing vaccines and autism. Is that an accurate characterization of the IOM's conclusions?

A No, that's not accurate at all.

Q What did the IOM say about further resources?

A I could read from the report. What we felt was that the real problems in the study of autism had to do with the fact that we did not understand the biology and the risk factors for autism very well, that it was very, very hard to even design epidemiologic studies that would target any groups, if there were groups, that might be at higher risk, and that to continually go back over and over looking at these studies of general population exposure and autism outcomes was (a) likely to produce the same results that the previous studies had done, and (2), it would divert -- I mean, these studies are incredibly expensive.

So for every million dollars or 2 or 3 million dollars that's spent on these large epidemiologic studies looking again at large populations, that amount of money that's not spent looking at the biology of autism, which we didn't

understand, and at the risk factors for autism, that we thought would yield greater understanding.

We did also think that once we had more knowledge from those sorts of studies, looking at the causes and the biology of autism, we could return to the field and design more intelligent, if it was indicated, more focused epidemiologic studies, if there was a plausible route to go. So we didn't say that money should be withdrawn. I think the exact language was something very close to, we think it should be funneled towards the most promising areas, and in the absence of understanding the fundamental biology of autism, it is very, very difficult to advance the science.

So it was an issue of prioritization.

Q Now, Doctor, you are an epidemiologist, correct?

A Yes.

Q What is epidemiology?

A It is the science of patterns -- the determinants of patterns of disease in populations and what we'll call the risk factors for those patterns, the determinants of those patterns.

Q And what role does epidemiology play in the community?

A Well, it's the only science that looks at an exposure and an outcome, the population patterns of exposure and outcomes in humans, and it's actually, epidemiologic-type designs are what undergird virtually all knowledge in medicine. When you look at the medical literature, almost every paper you read short of a case report, a single case report, can be characterized as some form of observational studies.

Of course, epidemiology can also be said to include experimental studies. Sometimes those are separated off. Experimental meaning somebody actually manipulates the exposure.

Q Now, is any epidemiologic study perfect?

A Perfect? Well, if the question is, can they be subject to reasonable criticism, absolutely, and the reason is -- and I am going to talk about epidemiology's observational studies. So observational studies are looking at the world as it is. Looking at smokers who smoke, not who are assigned to smoke, and looking at people who don't smoke because they don't smoke, and try to decide whether the differences in their outcomes are due to the differences in that exposure that they either chose, was chosen for them, or just happened to them.

The difficulty in epidemiology in all

observational designs is to figure out whether the differences you see in the outcomes are due to the difference in that exposure, or something about the people themselves that determined the exposure or is linked to the exposure. So, for example, if all tall people smoked and all short people didn't, in theory, we couldn't necessarily distinguish the effect of height from the effect of smoking when we looked at outcomes.

So there is always that residual question or doubt. In the example I just gave, you would begin to address it by looking at other studies where maybe there was a mix of tall and short people, or making the argument that tallness and shortness doesn't really make any sense, so I am going to down-weight that as a possible explanation, although you would of course want to do studies, measurements to confirm that, in fact, tallness or shortness was an unlikely and implausible explanation.

So every study can be subject to a criticism of this form in one way or the other, and in the end, the way epidemiologists have to approach this is doing multiple studies done in different ways, in different populations, sometimes measuring in different ways, and what you hope and what is believed in the field,

in fact, quite a lot of health policy and many things we do are dependent on this, is that the kinds of what we will call bias that any one study is prone to is not reproduced in exactly the same way in all the other studies.

In fact, this is one of the foundational principles. So we try to do studies, each of which address a relationship in a way where the amalgam of evidence is such that alternative explanations become increasingly unlikely.

Q Is epidemiology about statistics only?

A No. Statistics are obviously a very, very central and important part, but it's a marriage of the numbers that go with accounting in the populations with an understanding of underlying biology which allows you to design the study in the first place. You wouldn't even know where to start if you didn't have some sense of, you know, what's a relevant exposure, what's a relevant gene, what are the mechanisms, etc., etc.

Of course, you go into it not understanding those completely, but you have to have some sense of underlying biology. It also helps you decide when you get, you know, unexpected findings, which happens every day -- the journals are filled with them --

which ones are likely to be spurious and which ones are not. The ones that are likely to be spurious are the ones for which the underlying mechanism is opaque, unlikely or completely absent.

Every once in a while we are maybe surprised, but there are a lot of -- but biologic understanding is in every piece of an epidemiologic study from the moment you decide on the exposure, the patients, or the subjects, the outcomes, to the other side when you are analyzing the data.

Q What is required before an epidemiologist can reliably make a causal inference between an exposure and an outcome?

A To make a causal determination? Well, I pretty much outlined it. You want to see a relationship that's beyond the play of chance, in a variety of studies. You want to see a relationship where the, at a minimum, doesn't violate any biological or physical rules, and at a maximum, actually has a coherent biologic explanation behind it.

The larger the relationship, the less you might rely on the underlying biologic mechanism. So in the case of smoking, which is one of the signal epidemiologic triumphs, the relationship was so strong

and so compelling that even though they didn't understand completely at the time exactly how smoking caused lung cancer, it was very, very hard to resist the relationship, and it was seen in so many populations, it was very hard to construct plausible, competing explanations for what was being seen, and there was some laboratory and mouse and other evidence that made it plausible.

But in most cases, as the relationships that you see are weaker, still, they have to be beyond the play of chance. The corresponding biologic explanation has to be that much stronger. So it's sort of a, it's a marriage between the strength of what we'll call accounting evidence and the strength of the explanatory evidence behind it. The weaker the accounting evidence, again, it still has to be beyond the play of chance, the stronger the underlying biologic theory has to be.

Q Doctor, why is epidemiology particularly suited to addressing questions such as the relationship between thimerosal-containing vaccines and autism?

A I actually want to go back to the previous question a second, but I'll answer -- restate this question?

Q Certainly. Why is epidemiology particularly suited to the question that's before the Court today, a relationship between thimerosal-containing vaccines and the outcome of autism?

A Because it's the only science where it looks, as its exposure, thimerosal exposure, and as its outcome, autism, this is the science that looks at that. Any other science is going to involve a much smaller piece of that chain and involve some sort of speculation about what the other pieces might be that aren't being studied, but it's only epidemiology, looking at the patterns in humans and human populations, where we really address the central question that we faced in the committee and that I gather is faced today, which is, if a human being is exposed to thimerosal, is there a higher risk of autism at the other end?

I can't think of any other methodology that one would use to address that complete question in human beings.

Q Now, it's been said that there is a dichotomy between laboratory science and epidemiology, and I believe you said earlier that epidemiology is itself a science, correct?

A Yes, it is.

Q Okay. Now, you wanted to go back to the previous question?

A Yes, I just wanted -- you said, what do we need to make a causal conclusion, so I said it had to be beyond the play of chance, and I just wanted to tie in my previous answer, and you had to effectively rule out alternative explanations for that observed relationship, which we do, as I previously explained, by doing many different kinds of studies in different ways.

Q Now, there was a lot of information presented to the IOM in 2004.

A Yes.

Q But how many epidemiologic studies alone did the IOM consider in 2004?

A I think it was five or six.

Q And how many epidemiologic studies have come out since the IOM in 2004 issued its report?

A I think it's four.

Q Now, getting back to the conclusion that the IOM made in 2004, was it the strength of the evidence that led you to conclude that it favors rejection?

A Yes.

Q Is that my understanding?

A Well, it was a combination of the strength

of the epidemiologic evidence and the absence of any laboratory or mechanistic evidence that would controvert that conclusion.

Q Now, Doctor, I'd like to talk about Dr. Greenland's opinion that he has rendered in this litigation. Have you read his report that's been --

A Yes, I have.

Q -- that's been filed in the King case's Petitioners' Exhibit No. 4 and the Mead case, it's Petitioners' Exhibit No. 18?

A Yes.

Q And did you listen to his entire testimony he gave in court last week?

A I did.

Q What do you understand his opinion to be in this litigation?

A I think it can be, well, I'll refer first to his written report and then his testimony, simply that the existing epidemiologic studies don't rule out the possibility that there is some subgroup, a small subgroup, that could be at elevated risk due to thimerosal, and that the epidemiologic studies, in a sense, dilute the effect that might be seen in that subgroup by including a large number of other subjects whose risk would not be raised by thimerosal, and it

really just comes down to that.

He just says that that is possible, and I don't disagree with that. I could have written it myself. In his testimony, he -- well, I'll let you ask the questions. That was as far as he went in his written report.

Q And do you understand him to now be limiting his opinion to a possible subgroup known as what he terms 'clearly regressive autism'?

A Yes, that's how he specified it in the report.

Q In his testimony as well?

A Yes.

Q Now, Doctor, in your report, you talk about mathematical bounds in epidemiology. Could you please explain what mathematical bounds are?

A Well, they can apply to any number. The bounds that he calculated were basically the approximate limits for how high a risk might be in that subgroup that's still compatible with the largely negative evidence that he actually acknowledged in his report. That was the other thing I meant to say, that he did not contest the overall summary of the evidence as put forth by the IOM committee, nor did he take issue with that in his testimony when he said,

overall, he felt that the elevated risk, or the risk due to thimerosal in the general population was small or nil.

So he specified that, and the mathematical bounds refer to, with the residual uncertainty, there is always uncertainty in any estimate. For example, if there was zero, if we knew absolutely for sure there was zero effect, which I think is quite likely, but we don't know for sure, out of any epidemiologic studies or combination of epidemiologic studies, what we would expect to get is an effect estimate of zero, that's what we would see, with plus or minus something.

So someone can always look at the plus or minus and say, aha! There's room in that plus or minus for somebody to fit in there.

Q Is that what Dr. Greenland is doing in this litigation?

A Effectively, yes. So there is -- but I want to make the point, even if the point estimate, that is, our best guess of what the risk is, is exactly zero, there is always going to be some imprecision around that, by definition. We use finite populations. Even though the populations looked at here were in the hundreds of thousands, there is

always some residual uncertainty, and so you can always, by definition, say that you haven't ruled out the possibility of a positive effect.

The only way you can literally rule out the possibility of a zero effect is to prove the existence of a protective effect. That's the only way, mathematically, we could do it. So it's always going to be the case, if we get mathematical estimates that include a zero effect, that that will go a little bit further and we can fit a high-risk small subgroup in that and say, ah, we couldn't see them.

So what he did is he took the upper limits on what are called the confidence intervals or the precision around various estimates, and he did this for studies individually, and he said, well, if clearly regressive autism only makes up a small portion of the population -- and I think he first used 10% and then Dr. Fombonne suggested 6%, but it's not that important -- you could fit in an elevated risk in that small group and still be consistent with the evidence because the evidence has that imprecision, even though it actually, given the confidence intervals we have right now, they don't go much above a zero effect or much above 1, 1 being the rates are equal in two groups.

So that's basically the argument he makes, that it's mathematically possible, and that mathematics is correct. It's algebra. I could say the same thing. So where he doesn't go, and which is really the point of my report, is from the possible to the probable. That is, it's one thing to say it could be true, but where we really want to go, and what the IOM committee felt it had to opine on, was, is it likely?

And that's where we came down on the other side, and he actually does not offer an opinion in his report as to whether it's likely, and when you asked him what his specific opinion was, he said he had no opinion one way or the other. So he was being -- that was exactly right. He wasn't opining on whether it's likely or not, only that it was possible, so I thought his answer to that question was quite reasonable, and expected.

Q Now, in your report, you talk about the way in which the confidence intervals are two-sided, and I believe you touched on it.

A That's right.

Q But could you further explain what you mean by being two-sided?

A Right. So the confidence intervals are the

imprecision. They give the range of true relationships that are consistent with the data. They go up above zero, or zero effect, and they go down below. So one could equally say, just based on math alone, that a strongly protective effect, or a protective effect, is also possible, it's equally as possible as a risk, as an excess risk.

So the math itself, just alone, doesn't differentiate between the plausibility of a strongly protective effect and a risk effect, and what's of interest is almost all the studies, the larger studies, show as their best guess, surprisingly, and effect in the protective direction, a little bit.

Q You are talking about the studies that have been done looking at the relationship between thimerosal and autism?

A Yes, the epidemiologic studies. Most of them show estimates showing some degree of protection. Now, do I necessarily believe that? No, I don't necessarily believe it's protective of autism, because I don't think that that's particularly -- I don't think there is any biologic basis for saying, you know, you would want -- that exposure to mercury in that form would protect you against autism.

So the reason we don't say it's protective

is partly because we don't believe it has very strong biologic plausibility, but in lieu of saying it actually favors protection, at least we don't think that it causes excess risk. That is, we think it favors no effect at all, and that's, again, what the IOM committee said.

Q Doctor, taken together, what do the epidemiological studies demonstrate with regard to a purported autism epidemic in this country related to thimerosal-containing vaccines?

A Well, again, here Dr. Greenland and I are in accord. He said that any effect due to thimerosal would be nil or small, and all the epidemiology having to do with the rates aside, the epidemiologic studies looking at the effect of thimerosal basically rule out large increases. What they don't rule out, again, are these very small subgroups, but you can't have it both ways.

So they make thimerosal as a possible cause of a many-fold increase in autism virtually impossible.

Q Now, in your report, you state that Dr. Greenland's argument requires that thimerosal only raises the risk of regressive autism, or --

A That's right.

Q -- even really regressive autism, with no effect on any other form of autism.

A That's right.

Q Could you explain what you mean by that?

A Yes. So this is an example of how one can do math. So he calculated these bounds saying, well, let's imagine that this exposure just raised the risk of regressive autism, which we'll say makes up something between 5 and 10% of the population. So that excess could be swamped by no effect in the risk, and so the effect estimate in the population could fit into this little bit of uncertainty about, you know, could it go slightly in the positive direction.

But that calculation that he did, and again, he acknowledged this in his testimony, assumed that it had all its effect only for children with clearly regressive autism, and zero effect in the other 90 to 95% of the population, because if you had some of the -- you wouldn't even have to have all of the effect in the population. You could have a five-fold effect in one group and maybe just a two-fold effect in the rest of the population. Well, then you would see that.

We would have seen that in the epidemiology. So this speculation, this calculation, to the extent it has an applicability to the real world, absolutely

requires that most or all of the elevated risk is restricted just to this one subtype, and none of that excess risk is shared by anybody else. So he is positing really a dramatically different causal pathway, in a sense, that it's only a trigger for this, it's not a trigger for that, and again -- well, just that.

So that's the basis for his calculation. As soon as you start to allow a little bit of extra risk for everybody else, then that's basically ruled out by the epidemiology because that would be revealed in the general population patterns. So that distinction, as I pointed out in my report, to even be a starter requires some sort of biologic or mechanistic justification as to why in regressive autistics we would have a very, very different causal pathway, that they have a fundamentally different biology than children who don't present with that phenotype, and he doesn't present any evidence to that effect, and in his testimony he said he didn't know of any evidence to that effect.

So whether that's possible, I guess it remains, in the theoretical mathematical realm, possible. It's possible. Whether it's probable, well, there was no evidence presented. And again,

this is what the IOM committee had to deal with, exactly this sort of argument. This was acknowledged in the report as something that always, you know, the kind of argument that can always be made.

Q Now, Dr. Greenland in his report and during his testimony, he used the analogy of cancer --

A Yes.

Q -- as an example of a broad disease category within which exist distinct types of cancer that have different causes.

A Right.

Q Is this a proper analogy to use?

A Well, it's a great analogy to use, because it --

Q Why is that?

A -- absolutely supports my point. Well, let's just look at leukemia. I think he mentioned leukemia. If you asked me, as you asked him, can you distinguish biologically between a child with regressive autism and a child with non-regressive autism, is there any test you could do, any x-ray, anything, any evidence -- now, he's not an expert in autism, but he said no, he didn't know if he could do that, and the literature does not say that we can do that.

So those two subtypes are not distinguishable biologically. If you said to me, can you distinguish lymphocytic leukemia from myeloid leukemia, I would say, well, yes. Lymphocytic leukemia affects lymphocytes. You can look at a slide. That's where it gets its name. Myeloid leukemia affects myeloid cells. You can look at a slide.

We know the biology of lymphocytes. We know the biology of myeloid cells. It's completely plausible, in fact expected, that the risk factors, the course, the treatments, all the clinical features of those two diseases would be different, and in fact, they are. We observe that they are. There are many, many aspects of those two diseases that are different. If you asked me the difference between bronchogenic carcinoma and non-small cell lung cancer, all you have to do is go to the pathologists.

Say, you know, if you ask the question, are they biologically different, yes. They are biologically different. They affect different cells in different places. So if you ask the question, are those biologically different, can you tell me biologically what's different, Doctor, about that form of cancer from that form of cancer, I would be able to

explain it, and that's what makes different risk factors, different course, different treatments, completely plausible in the cancer realm.

We don't have the same situation in the autism realm. There may be a day when we understand it better and we do understand what the classifications are. They may have nothing to do with how it presents. It may have things to do with things that we can't even imagine today. So the key issue is, is there any evidence that these two forms -- we'll just call them regressive and non-regressive. We won't consider those with epilepsy and those with not, or those with more severe problems or those with not, we'll just consider that particular phenotype. Is it causally different?

That is, is there reason, strong reason to believe that there is a different, completely different causal pathway such that this alleged, purported risk factor would cause a high risk in one and zero risk in the other? Our understanding is not there. There is no current evidence that that is the case. I cannot predict what we will know in the future.

Q Doctor, your report discusses what the results would likely be if a meta-analysis of this

study had been done.

A Yes.

Q First of all, what is meta-analysis?

A Meta-analysis has two parts. One is quality assessment, that is, a systematic and close look at the studies themselves, and then if you deem them to be combinable, it's really just in a sense an adding up of the studies, and the precision of the combined estimate is almost always more precise than either study taken alone. So if we have situations, like we have here, where you have lots of estimates that are just a little less precise than you want, if you can justify their pooling, then your combined estimate will be much closer, you know, the plus or minus will be a lot tighter than it would be if you just look at them separately. So that's what meta-analysis is.

Q So in your report where you discuss what would likely be if a meta-analysis of the epidemiological studies that have looked at thimerosal-containing vaccines in autism, what would a meta-analysis likely show?

A Well, because most of the point estimates in the larger studies were under 1, they would show that the upper bounds, those upper confidence limits which Dr. Greenland took separately, were probably a lot

closer to 1 than they look like when you look at the studies separately. That said, the reason the IOM committee didn't do that is because there can always be challenges to, well, exactly how comparable is this study to that study, and can you really liberally add them up?

So as soon as you get into that exercise, you invite those criticisms, so what you can say qualitatively is, again, when you see a whole series of studies done in different ways that have limits that are only slightly above or moderately above 1, you can say that combining them will make them more precise and probably the upper limits closer to 1, or closer to a zero effect, but we didn't do that quantitatively because you would get lots of arguments over exactly where that upper limit is, and given that the evidence clearly did not show a relationship, we didn't need to do that to come up with the conclusion that it favored no relationship.

Q Now, Dr. Greenland did not file a rebuttal report in this litigation, but he did offer some criticisms of your report when he testified orally here last week, and one of the criticisms that he said was that you failed to account for potential problems that you cited in your report, that you presented no

further analysis to show that the studies ruled out subtype effects. Do you have any comments as to that criticism?

A Well, first of all, as he said and we all know, these subtype effects were not measured in those studies, so I couldn't do those analyses, but on the other hand, no evidence was presented that would make those subtype effects likely or plausible. So it's true that one cannot literally rule out that possibility, but the question is, what is the evidence that makes it likely in the first place? So --

Q And did he offer any evidence as to --

A And he didn't offer any evidence to rebut. So it still remains, as I said before, it is possible, certainly mathematically possible. Whether it is likely or probable based on what we know, both biologically and the limitations of what we know, that's another question, upon which he did not opine. So he didn't, in the end, in spite of my not showing evidence against that possibility, when asked directly, he said he had no opinion one way or the other.

So he actually didn't offer that his conclusion based on the speculation that it might exist resulted in a likely or probable conclusion that

it did.

Q Now, during his testimony last week, Dr. Greenland also took issue with the example in your report of PETA's analysis of astrologic signs. He was saying that TCVs have no resemblance to astrologic signs and he called it rhetorical nonsense. Could you explain whether you think that analogy is relevant to this litigation?

A Well, I don't know about the rhetorical nonsense, but I'll explain about the example he said, and he's right, that it's a famous example, and it's a famous example for very good reason. It illustrates a foundational principle about why you have to have biologic plausibility to make a finding credible. So the basic principle underlying that example -- and it was somewhat different than here, I'll explain why in a second -- was that they had this study that looked at treatments for, it was heart disease, and they did this analysis that showed a subgroup effect that showed it had no effect in, I think, 11 of the astrologic signs, and all of the effect was grouped under Virgo, or I can't remember what exactly I said in my report, but one of the astrologic signs, and they did this twice, and this obviously is not true, and they presented it this way to basically discourage

people from looking for subgroup effects in an overall population that didn't have any strong biologic foundation.

But what was different about that situation than here -- so that was the principle that was being demonstrated. It didn't matter that it was in a clinical trial. It didn't matter that there were multiple subgroups. The point was, in that situation, there was actually evidence, that is, you actually could look at the relationship under Libra or Virgo and see that it's a certain size, and look under all the others and see that they are zero, but you wouldn't believe it and you would think it is implausible because there is no biologic underpinning, there is no support.

In this case, it actually doesn't even advance to that point, because it isn't the case that we have evidence, empirical evidence of a relationship that we say we are going to believe or not believe based on the biology. We don't see anything, and the contention is, well, maybe you would see something if you divided things up, if you looked at the subgroup. So we don't even have that subgroup to look at.

That's acknowledged, but the question has to be, well, even before you do that, what's the

strength, you know, what biologic reason would you have to make that distinction in the first place. Like, what biologic reason could you have to make between the various astrologic signs? So that was the point. The point was that the math doesn't tell the story all by itself, that you must look at the cogency, the empirical support of the mechanism underlying any patterns that you see.

Again, in this case, we actually don't have a pattern that we have to explain away because it's not biologically plausible. We actually don't have a pattern, and what's being claimed is, maybe there is something underneath that pattern that we don't see. Maybe there is a subgroup for which no biologic evidence is offered. So the point of the example was simply to say that it is very important to have some degree of biologic, mechanistic rationale to support a hypothesis, even to begin exploring it, and that just puts it in the realm of the possible, and then you look for information that puts it in the realm of the probable.

Q Now, Dr. Greenland also said in his testimony that it's unscientific to assert that there are no differences in mechanisms when there is no understanding of the mechanism, and he accused you of

invoking fictional scientific principles, that you were presenting absence of evidence as if it were evidence of absence. Is that what you are doing here, Doctor?

A I don't think so. I am completely open to this being empirically demonstrated, if it ever is. He raises a possibility. If the scientific community takes this hypothesis seriously enough, and it might take it seriously enough simply because there is so much concern about it, for the same reason that they took the thimerosal-autism hypothesis seriously in the first place, even though there wasn't much biologic evidence to suggest that it was true, but just the concern about it often generates the need to, you know, go out and do a study that specifically addresses that.

But I would say that it's a curious statement when one is positing no evidence for it to say that it stands and is probable because somebody else cannot offer any concrete evidence against it. The fact is, we do have evidence from overall populations that shows no effect. That's very much like what we see in medicine when we do clinical trials and we try a therapy, and you know, if 60% of people survive in one group and 40% of people survive

in the other group, we say that therapy works.

It is always possible for someone to come in and say, oh, it doesn't apply to this kind of person. Generally, what we find, particularly when there is no biologic reason to say why that person is different, very, very frequently in medicine we find that these claims of subgroup effects don't hold up, and this has been empirically studied. So when we have consistent demonstrations in overall populations and no compelling or demonstrated biologic distinction between members of those populations, we generally accept the population average as the most likely one.

It does not rule out the possibility, again, as I said from the start, that there could be a different effect among members of that population, but I don't think it's very fair to ask that there be specific rebuttal of that when there is no evidence yet for it. Whether this hypothesis is strong enough to merit going out and spending money and mounting the studies to explore it is a very reasonable question that I am sure the scientific community will take up, and maybe the study will be done, but I don't believe the hypothesis remains likely or probable in the absence of evidence against it, particularly with no biologic supporting evidence.

It remains as a hypothesis that is not specifically -- as a possible hypothesis that, as yet, is not specifically rebutted by the extant evidence that that is true. But I didn't say that it couldn't be true, or that I had specific evidence against it, except against this general background of invoking subgroup effects when there is no compelling subgroup biology as of yet.

Q So does Dr. Greenland in this litigation, does he state that thimerosal-containing vaccines cause clearly regressive autism?

A No, he did not.

Q Does he state that thimerosal-containing vaccines are even a most likely cause of clearly regressive autism?

A I don't believe he said that, no.

Q Does he even establish that clearly regressive autism is a disorder category that is recognized by the scientific community as having a different biology or different causal determinant?

A No, he said that he could offer no evidence to that effect.

Q And does Dr. Greenland offer any evidence that thimerosal-containing vaccines elevate the risk of clearly regressive autism?

A No, he didn't.

Q Finally, Doctor, why are you testifying in this litigation here today?

A Yes, well, some people ask why I served on that committee too. I think, I mean, this is clearly an area of tremendous concern, a tremendous amount of heat, but if scientists looking fairly at the evidence, absent the crucible of concern and -- don't speak out on what they, looking at it objectively, actually see in the evidence, I feel like in some way they are not doing their job.

They are not serving the vast majority of people who very much want to do the best thing for their child, and simultaneously for those parents who have autistic children, want to feel like it wasn't something they did that caused their child's autism, and so I think I feel that it would be very easy to duck these types of activities, but it wouldn't serve the public health, and it wouldn't serve the really very sincere, very sincere concern of parents on all sides, to not say honestly what we think is the most likely message from the evidence that occurs today, and at the same time, help -- and this is what we did through the IOM, not necessarily here -- point the way for further research that might elucidate the causes

and cures or treatments of this really very, very difficult disease.

So I think -- just that.

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

SPECIAL MASTER HASTINGS: All right. Do the Petitioners have any questions of this witness?

MR. WILLIAMS: Yes, we do.

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

MR. WILLIAMS: Can I have just five minutes to get organized a little bit?

SPECIAL MASTER HASTINGS: Certainly you may. We will take a five-minute recess.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: Please be seated. All right, we have Dr. Goodman still on the stand, and Mr. Williams is going to ask some questions. Go ahead, sir.

CROSS-EXAMINATION

MR. WILLIAMS: It's still morning. Good morning.

THE WITNESS: Is it? I've lost track of time.

//

BY MR. WILLIAMS:

Q I want to ask you first about the journal about clinical trials and clinical trials in general. You list your editor-in-chiefship of the journal on clinical trials as the first thing on your CV under your editorships, and you mentioned it today in your direct as one of your qualifications.

A Uh-huh.

Q How long have you had that position, editor-in --

A That, since 2004.

Q Your CV says since 2003.

A I was appointed in 2003, but didn't officially take -- well, let's see, what's today? No, I think it was since 2004, because the journal, what happened was, it's a society journal, and it changed its name and publisher in 2004, I believe, and that's when I took over. It was the same journal. But I was appointed in 2003, so maybe there is a slight discrepancy there.

Q Okay, and it is the *Journal of the Society for Clinical Trials*?

A Yes.

Q That's the official name?

A Uh-huh.

Q Now, the Society for Clinical Trials, is that based in England, or?

A No, it's actually -- well, it's an international society but the main office happens to be in Baltimore, and it involves folks from government, from industry, from academia, interested in clinical research methods in general, not just clinical trials.

Q Do you ever have to go to meetings as part of your job as editor-in-chief?

A Yes, I just came back from one yesterday, or on Wednesday.

Q And does the society pay for your travel in those instances?

A No.

Q You have to pay for it yourself?

A Yes.

Q Do you get any staff support to run this journal?

A I have a managing editor that is paid for by the publisher that -- just 20% of her time.

Q There are corporate sponsors of the journal, aren't there?

A No.

Q Of the society?

A No -- oh, of the society? Not formal sponsors. I think they maybe get corporate contributions to their meetings, but it's not a corporate society by any means, but I think they -- when I was just at the meeting, they had a list of contributors and it included both academic and corporate sponsors.

Q We have a --

A Oh, there it is. Yes, okay.

Q -- page from the website here. I just wanted to point out that two of the corporate sponsors of the Society for Clinical Trials are major manufacturers of vaccine. Did you know that?

A I didn't -- I honestly don't pay attention to who helps support the meeting, no, but I did know that there were corporate manufacture -- I mean, I did know that they get some money to help support the meeting, yes.

Q Do you ever do consultancy with drug companies on clinical trials, independent of your role as editor-in-chief?

A I may have in the past, on the design of clinical trials, but honestly, I don't recall -- I might have visited a company about 8 or 10 years ago about the design of the clinical trial, but I don't

honestly recall. I think I did, but I don't remember what the trial was, and I don't honestly even remember what the company was.

Q When, you know, the 2004 IOM report that you talked about?

A Uh-huh.

Q There's a statement in there that says that none of the members of the committee had any conflict of interest.

A That's right.

Q And you don't consider having vaccine manufacturers as the sponsor of the society that publishes your journal to be a conflict?

A Well, they support the -- first of all, I was -- they support the meeting. They don't support the society specifically. We are completely -- this has no bearing on the activities of the society. No. The answer is no.

Q Okay. When you picked the astrology example, we didn't have a report yet from Dr. Kinsbourne. Have you read his report?

A I have looked through it, yes, but I can't say that I read it carefully or that I am expert in that area.

Q And I take it you haven't reviewed the

infant monkey study that shows the inorganic mercury goes to the brains of the --

A I read the study, yes. Again, I'm not expert in this area. I didn't notice that they connected this with autism. It seemed that there was a study about the entry of mercury into the brain of these infant monkeys.

Q Is it still your opinion today that the biological plausibility that thimerosal-containing vaccines could cause regressive autism in some kids is as silly as astrology?

A I never said it was as silly, but I said in order to elevate that from the possible -- I don't say that it's not -- it's not literally impossible -- to the probable takes a combination of both empirical, counting knowledge accounting knowledge and a more complete or more accepted theory than we have today.

Q But you haven't analyzed Dr. Kinsbourne's report or the underlying studies that he cites.

A Well, I rely on the scientific community to judge whether that hypothesis that he has published -- has he published that, I'm sorry.

Q He hasn't published it in the --

A Well, the scientific community then hasn't weighed in on that. I would depend on them, and if I

was part of a committee assessing the body of evidence, I would look at both his published paper and I would look at the response of the scientific community to that paper to decide how much weight to give it. I wouldn't necessarily be the expert evaluator myself.

Q You realize that in this vaccine court that we are in that it's very rare that the cases get written up and published in the peer-reviewed literature, don't you?

A What cases?

Q The cases that these Special Masters hear about alleged injuries from vaccines.

A Right, but I assume that the underlying principles upon which you are making a judgment are principles that have relevant science that appears in the scientific literature.

Q In the four or five studies that the IOM committee had in 2004, most of them were ecological studies, weren't they?

A There were three controlled studies. I think there were five altogether. Two or three were ecological studies, and two or three were controlled studies. Yes, that's right.

Q And in your report, you state that the

studies taken together provide strong support that there is no causal connection between --

A Yes.

Q -- thimerosal vaccines and autism in general.

A Yes, right.

Q And you are using ecological studies as part of that strong support?

A Yes.

Q You don't have any doubts about ecological studies being --

A Well, I do. I mean, I think reasonable people could disagree on whether it's strong or moderate. It's still support for the hypothesis that there is no relationship. Any qualms one would have, I'll talk about those in a second, about those studies wouldn't magically turn it into a positive relationship. The IOM didn't put a particular adjective on it. They said, favors a no causal association. I would absolutely subscribe to that. Personally, I find the nature of the fragmentary biologic evidence and very, very consistent evidence of continued high rates in populations that get zero thimerosal in their vaccines to be fairly compelling.

Now, to comment on the ecologic studies,

ecologic studies are absolutely subject to a variety of criticism bias more than controlled studies, and they are not as strong as the controlled studies that we looked at. However, in the situation where the exposure from vaccines goes to zero, or effectively to zero, very close to zero, and rates still seem to continue completely unconnected with that, those are subject to less concern than the kinds of ecologic studies where you just have two phenomenon co-varying in a general sense.

But the general point you make is right. Those are weaker studies than the controlled studies, but it certainly is extremely interesting that the autism rates are virtually unaffected, and even seem to go up, at least as they are measured -- I won't talk about what the true rates are right now -- in a context where thimerosal exposure has gone to zero in other countries and has been very, very low here.

Q And I know you admitted this on direct, but just to reiterate, none of those studies tried to measure clearly regressive autism?

A No, I am not aware of the fact -- I don't think they broke that out, no.

Q We don't really know what the rate of clearly regressive autism was in any of those

countries, nor in California.

A No, and let me point out that there is a reason why, and the reason this doesn't lessen, the fact that that evidence doesn't exist, is that when people design studies, they measure all sorts of things. They could measure -- if we did a study in this room, we could measure the number of lights and the nature of the wood and the height of everybody at this table.

We could go crazy with a data set. We can measure literally everything, but you have to restrict the things you measure to the things that you a priori think are reasonably possible or plausible, and the reason that people didn't make that choice when they designed those studies is because this hypothesis was not out there and there was not a strong or even existing biologic reason to distinguish between the two.

So it's not a complete accident that that information is not there. It's because there wasn't the biologic suggestion that that would be a meaningful breakout, and it would be very, very hard methodologically, as I'm sure Dr. Fombonne will testify, to make that determination. It's hard, I believe, even in an individual case, often. You have

to have a lot of documentary evidence to distinguish clearly regressive from non-clearly regressive.

So that would be an extraordinarily difficult study to do. I'm not saying it won't or shouldn't be done, but the reason the evidence isn't there is because the designers of the studies either couldn't get the information or it would be very difficult to get the information, and there was not, and is not at the moment, a very strong biologic reason to do so.

Q You've talked to Dr. Fombonne about what he is going to testify?

A I have only read his expert report.

Q Okay. Do you have an opinion as to whether the increase in autism rates in California or elsewhere is real, or is it just, you know, an artifact of the diagnostic methods?

A I would say that Dr. Fombonne is far more expert than I in that area. We did look at it at the IOM. I personally believe that it is -- if rates are going up at all, and I think that is a question. I think there is, without a doubt, they are not going up in the multiple, you know, fives, tens, that have been drawn on curves. That is almost certainly not the case.

Whether they are going up at all and exactly how fast they are going up I think is an unsettled scientific question, and I don't have enough special expertise to distinguish between going up some and going up not at all. I believe very strongly that it's not going up in the exponential, astronomical way that has been portrayed, particularly in the lay press and to some extent in other settings. I think that that's pretty certainly not the case.

Q In preparing for your testimony, did you review the NIEHS expert panel's report on whether and how studies could be done in the Vaccine Safety Datalink to explore the question of whether thimerosal-containing vaccines are associated with autism?

A No, I did not.

Q Are you aware that such a report was written?

A No, I am not. When was that written?

Q Let me show it to you. This is -- we have a copy. I can give a copy to the witness.

A Do you have two?

Q I don't have two with me.

SPECIAL MASTER HASTINGS: Dr. Goodman, we are starting to get a little feedback from you.

THE WITNESS: Oh, sorry.

SPECIAL MASTER HASTINGS: And I wonder if you, I'm thinking you may have gotten a little closer to the mic than you were earlier.

THE WITNESS: Okay. I'll sit back here and pump up the volume.

BY MR. WILLIAMS:

Q We are going to get a copy for you to look at --

A Okay.

Q -- and get the exhibit number, but let me tell you just briefly what happened, and I'll show you this in the text in a second. The NIEHS in 2006, now almost two years ago --

A Okay.

Q -- convened a panel of experts on autism and epidemiology and toxicology and asked them, they actually spent a couple days meeting and listening and presenting on whether or not it made sense to do some studies using the Vaccine Safety Datalink to try to look for an association between thimerosal vaccines and autism.

A Right, okay.

Q And they actually ended up recommending that two specific studies be done.

A Okay.
Q You weren't aware of this?
A No, this is not my field.
Q Okay, well, let's --
A So I haven't followed it -- I followed the evidence to 2004. I've reviewed the epidemiologic studies since then. I have not followed all the things that have gone on since that time.
Q What you see on the screen now is the first page of this report. You see that it's signed by the director of NIH --
A Yes.
Q -- in October of 2006?
A Okay. It's very fuzzy on my screen, but I'll take your word for it. It does look like a live survey, yes. Ah, and that's his signature.
Q This is Petitioners' Master Reference List 553 --
A Okay.
Q -- is the exhibit. Now, I want to turn to the page that lists the experts who were convened. It's about six pages from the back. I think you'll probably know some of them. Okay, here it is, and blow up the top four first, Scott, and then we'll go to the bottom four. Do you know Dr. Hertz-Picciotto?

A Yes, we've served on the IOM committee Veterans' Agent Orange together.

Q And you said you've read Dr. Burbacher's study on the monkeys, right?

A Yes.

Q And what about the other two people there? Do you know them?

A I don't know them specifically, no.

Q Okay, let me show you the other names. Dr. Davidson or Dr. Factor-Litvak?

A No.

Q All right, and then two more.

A Well, I know Craig Newschaffer very well.

Q Okay.

A And I don't know the other one.

Q And of the people that you know that are on there, do you respect them as epidemiologists and scientists?

A Yes, absolutely, yes.

Q Well, let me show you what they recommended be done in looking at the VSD. Now this is -- this page. The first page of the executive summary.

SPECIAL MASTER HASTINGS: Is that page 7 of the exhibit, I think?

MR. WILLIAMS: Yes, page 7 of the exhibit,

and it's the last paragraph I wanted to blow up.

BY MR. WILLIAMS:

Q This is from the executive summary and it says -- first of all, they were asked, could we do an ecological study just looking at the rates of autism from one year to another, and they decided there were too many confounders to recommend doing that.

A Uh-huh.

Q But they did view positively, it says, an alternate future study design that was viewed positively among panel members was a study of a high-risk population, defined in this instance as siblings of individuals diagnosed with AD or ASD, and they go on to describe that. You are aware of these kinds of twin or siblings studies, aren't you?

A Yes, I think this is actually a good idea.

Q Yeah, and then there is also a recommendation in the bottom half of this paragraph for an extension. It says, another possibility that generated support by the panel, if you could highlight that, Scott, right here in the middle. Yeah, there we go. Another possibility that generated support by the panel was an expansion of the VSD study published by Verstraeten back in 2004. That's one of the studies that your IOM committee had relied on.

A Yes, uh-huh.

Q And what they say was the availability now of several additional years of VSD data provides an opportunity to provide a more powerful test of any potential association. And then they also talk about a retrospective cohort using the California MCOs or DDS. Do you agree that those studies would also be a good idea?

A Probably. I mean, I'm not dealing with the budgets and trying to prioritize according to what other studies would or would not be done, but those do look like very good ideas. The IOM committee itself recommended further research in high-risk populations, and this is a good high-risk population.

Q Now, unfortunately, the Bush Administration has not chosen to fund these studies, and they haven't begun yet, but we wanted to show you that the Petitioners' Steering Committee did try to get access to this. Let me show you a motion that we filed in this litigation in this court back in '06, right after this expert report came out. Did you know that we had filed a motion on behalf of the families we represent, about 5,000 families?

A No, I didn't know.

Q And that we had a panel of Dr. Greenland,

Dr. Kinsbourne, Eric Gershwin from UC Davis, and --

MR. MATANOSKI: Your Honor, I'm just going to ask for a proffer of the relevance of this. I believe this motion has already been ruled on by the Court.

SPECIAL MASTER HASTINGS: Well, it has. I'll give him a little latitude here.

BY MR. WILLIAMS:

Q Well, wouldn't you agree that one of the reasons we don't have epidemiological studies that address the question at hand here is because the government has blocked us from getting those studies, even though they have been recommended by an NIH expert panel?

A I have no basis on which to render an opinion on that.

MR. MATANOSKI: And I'd actually have to object to that characterization.

SPECIAL MASTER HASTINGS: Well, it's already been answered, so.

MR. MATANOSKI: I just meant to object to that characterization of what the government has done.

THE WITNESS: I just want to say one thing. In my comment that I thought it was a good idea, I have no information about how much it would cost, you

know, what the choices are really to be made. In theory, if we had a good study of those, you know, maybe it could provide interesting information, but I have no access to any of the real-world considerations that went into any of the things that you are discussing.

BY MR. WILLIAMS:

Q Now, you said that this postulated group of affected kids that have clearly regressive autism from thimerosal-containing vaccines would be a small group, you said?

A Yes, I followed exactly what Dr. Fombonne and Dr. Greenland said.

Q I want to just do one little --

A A small portion of the total group.

Q Right.

A Yes.

Q I want to do just a little arithmetic with you and then we will be done. There are roughly 4 million kids born every year in this country.

A Uh-huh.

Q You accept that? I mean, it would be a little --

A I will believe you.

Q Okay, and if you take the decade of kids

from 1992 to 2001 or so who got the biggest exposure from thimerosal-containing vaccines, we're talking roughly 40 million children in this country.

A Okay.

Q If the true rate of autism of all types was 1 in 150, which seems to be the number you hear most --

A Right.

Q Then, if thimerosal-containing vaccines were causing 10% of that, you know, could cause 10% of the total, which is the figure you sort of used as a compromise between Fombonne --

A I was just working off the numbers that are in the report.

Q Right, and you said it didn't really matter whether it's 6% or 10% because that's still too small for the studies at hand to pick up?

A Yes, the relevant number is the proportion of the total, because we have relative risks that apply to the whole population. So you are absolutely right, that proportion could apply to, you know, many, many, many children, but it doesn't make the math related to the relative risks and what can fit in, it doesn't change that at all. It doesn't matter whether that's 10 kids or 10 million, except if it's 10

million, you at least theoretically have the possibility of getting sample sizes to explore.

Q Well, if it was 10%, then the number of kids in the population who would have thimerosal-containing vaccine-related autism would be 1 in 1,500. Is that fair?

A Well, I'll just listen to your math. I'm not following all the numbers.

Q Okay, well, let me just summarize the math.

A I mean, you assume that it caused all of it, that you're just assuming --

Q No, no, no, now I'm assuming that -- let's take another assumption that the thimerosal-containing vaccines are only causing about one-third of this purely regressive group.

A Okay.

Q Okay, so now we're down to, from a population point of view, 1 in 4,500, and if you do the math, 40 million divided by 4,500, you come up with about 9,000 kids.

A Uh-huh.

Q Now, you still think that's a small group?

A The reference 'small' is the proportion of the total population and had to do with the mathematics of what you could detect given the

relative risks that we are observing. The 'small' did not, I never meant to, nor did I make any statement about the size of the problem or the number of children affected. I think it's quite clear that autism is a very, very big problem in this country.

It doesn't matter, actually, whether the rates are going up or flat, you know. One in 150 or 1 in 400 is actually a very high rate for a problem of this magnitude, so issues related to autism are important for exactly that reason.

Q And issues related to trying to figure out the etiology of autism are important.

A Oh, yeah.

MR. WILLIAMS: Thank you. That's all I have.

SPECIAL MASTER HASTINGS: Any redirect?

MS. RICCIARDELLA: We have no redirect.

SPECIAL MASTER HASTINGS: Any questions for this witness? Actually, I have one or two, Doctor. Now, you mentioned earlier that you had read the report of Dr. Kinsbourne.

THE WITNESS: I looked through it. I wouldn't -- read through -- I mean, it's not my area of expertise, and I was also aware --

SPECIAL MASTER HASTINGS: You haven't

studied it is what you are saying?

THE WITNESS: No, I definitely have not studied it.

SPECIAL MASTER HASTINGS: My question is, the way I read Dr. Kinsbourne's report, you, I think, accurately characterized what Dr. Greenland said. Dr. Kinsbourne went a little further than Dr. Greenland. As I read his opinion, I don't know if he used the word 'irrelevant,' but essentially, he says, because all these studies studied autistics in general and didn't focus on regressive autism, he said the studies are totally irrelevant to the Petitioners' theory here, which is focusing on causation of regressive autism.

THE WITNESS: Right.

SPECIAL MASTER HASTINGS: And I want to make sure I understood what you said today in terms of that issue. If I understood your testimony, and I want to summarize it and see if I have accurately understood it, you are saying that it is relevant because the studies don't mathematically rule out the possibility that there could be a very, very small subgroup that's highly associated, but you are saying it makes it seem -- because regressive autism, we don't see anything distinctly biologically different than non-regressive

autism, that it makes it seem very unlikely that there is an association with such a subgroup because we don't have any reason biologically to assume that there would be a difference?

THE WITNESS: That's pretty much exactly it. That is, the information on the overall relationship to autism in general and thimerosal is relevant to all children with autism until one can make and show, demonstrate empirically, that one subgroup is uniquely biologically different with respect to that causal factor.

So it is certainly relevant -- it is only irrelevant insofar as he can empirically demonstrate, that is, show that this is a unique biologic entity that's uniquely susceptible to thimerosal, where all other children with autism are not. So you described it pretty much exactly.

SPECIAL MASTER HASTINGS: All right, anything further based on that, Mr. Williams?

MR. WILLIAMS: Just one question about exactly this.

FURTHER CROSS-EXAMINATION

BY MR. WILLIAMS:

Q You wouldn't have to, for there to be biological plausibility of regressive autism being

different, it wouldn't have to be just thimerosal that could cause it. You could have other postnatal insults that could cause regressive autism, and it still be biologically plausible, right?

A I'm sorry, what would be biologically plausible?

Q That there is a susceptible subgroup of children who develop regressive autism from postnatal exposures to agents that persist in the brain and cause neural inflammation.

A First of all, I can't opine on that particular mechanism. There is a difference between biologically possible and biologically probable, so I can't opine on -- all I can say is that that particular theory is not yet out in the scientific literature, and other scientists haven't weighed in on it. I can't disprove it here, no, nor does the epidemiology disprove it. Maybe I'm not addressing your question. I'm sorry.

Q Well, for example, Dr. -- Sir Michael Rutter is going to come in here next week, and he's published his opinion, and he believes some cases of autism which are regressive because they are caused by postnatal infections can happen. I mean, he thinks it's biologically plausible.

MR. MATANOSKI: I'm not sure that's an accurate characterization of Professor Rutter's report.

SPECIAL MASTER HASTINGS: Let's suppose for a minute that it is. I understand the objection.

Did you understand the question?

THE WITNESS: Not entirely. Maybe I'm being dense.

BY MR. WILLIAMS:

Q Well, I thought I've been hearing you say that there just is nobody who thinks it's biologically plausible that a postnatal agent could cause regressive autism.

A No, I absolutely didn't say that. I said -- the question that the Special Master posed was that Dr. Kinsbourne said that the extant evidence was, in a sense, totally irrelevant to that particular hypothesis because they hadn't broken out specifically the regressive autistic types, and then he summarized his view of my testimony as saying it was relevant because there hadn't been a clear enough case made that this is a distinct biologic entity, and I agreed.

I am not testifying here today that there aren't people who say, or that it might not be true, that some environmental insult might play a part in

the expression or emergence of autistic symptoms. That's actually, I don't know if documented, but it's stated repeatedly in the literature that that's one of many possibilities.

MR. WILLIAMS: Okay. Thanks.

SPECIAL MASTER HASTINGS: Anything further from Ms. Ricciardella?

MS. RICCIARDELLA: No, sir.

SPECIAL MASTER HASTINGS: Any further questions from the Special Masters? All right. I guess we are done with you, Dr. Goodman. We thank you very much for being with us today.

(Witness excused.)

SPECIAL MASTER HASTINGS: Before we go off the record here, I understood that counsel had some matters they wanted to raise before we broke for the weekend. Now, I'm not sure what they were, and does anyone want to do those on the record, or do you want to do it back in chambers? Tell me what's going on here.

MR. MATANOSKI: I was the one who raised that there were a couple of matters to take up. I don't think they need to be taken up on the record.

SPECIAL MASTER HASTINGS: All right. If that's the case, we are going to break for the

weekend. For those listening in, we are done now until Tuesday morning at 9:00 a.m., so we will be adjourned until then. All right. Thank you all.

(Whereupon, at 12:30 p.m., the hearing in the above-entitled matter was adjourned, to reconvene at 9:00 a.m. on Tuesday, May 27, 2008.)

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REPORTER'S CERTIFICATE

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

CASE TITLE: In Re: Claims for Vaccine Injuries

HEARING DATE: May 23, 2008

LOCATION: Washington, D.C.

I hereby certify that the proceedings and evidence are contained fully and accurately on the tapes and notes reported by me at the hearing in the above case before the United States Court of Federal Claims.

Date: May 23, 2008

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