UNITED STATES
COURT OF FEDERAL CLAIMS

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

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Place: Washington, D.C.

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

Wednesday,
May 28, 2008

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

BEFORE: HONORABLE GEORGE HASTINGS
HONORABLE PATRICIA 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
12	3606	--	Eric Fombonne Slide Presentation

P R O C E E D I N G S

(9:00 a.m.)

SPECIAL MASTER VOWELL: Please be seated. All right. We are back on the record in the Theory II General Causation cases, and the Mead and King cases. And I see Dr. Lord is on the witness stand. And if you would raise your right hand.

Whereupon,

CATHERINE LORD

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

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

DIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Good morning, Dr. Lord. Would you please state your name for the record?

A Catherine Lord.

Q And would you please state what your current position is?

A I am the director of the University of Michigan Autism and Communication Disorders Clinic, and a professor at University of Michigan.

Q And would you please briefly describe your educational background since high school?

A I have a bachelor's degree in psychology from UCLA. I then went to graduate school at Harvard and graduated from the program in psychology and social relations.

I was an intern at the University of North Carolina. And I guess that's it.

Q Was that a postdoctoral position?

A Yes.

Q At UNC?

A Yes.

Q And do you hold any board certifications?

A I have, I'm an ABPP, which is American Board of Professional Psychologists in clinical psychology, and part of the National Health Register for clinical psychologists.

Q And do you hold any licenses?

A I'm licensed in Michigan and Illinois.

Q In what discipline?

A In clinical psychology.

Q And would you please briefly describe your academic employment history?

A My first position was at University of Minnesota, where I was an assistant professor in child development. I then went to Canada, to University of Alberta, with my husband. And then moved back to

North Carolina to set up a clinic at University of North Carolina in Chapel Hill. Then went to University of Chicago, and am now at University of Michigan.

Q And are you a member of any professional societies or organizations in your discipline?

A I'm a member of INSAR, the International Organization for Autism Research.

Q Is that formerly called IMFAR?

A Yes. SRCD, the Society for Research in Child Development. APA, American Psychological Association. That's probably the main ones.

Q And have you been honored for your work in autism specifically?

A Yes. I received an award from the Royal Academy of Psychiatry in the UK, and an award from California State, I was the chair of a National Academy of Sciences Committee looking at the effectiveness of early intervention in autism.

Q Now your report states that you are one of four scientists who make up the strategic planning committee for autism research for the National Institutes of Health. What does that entail?

A As part of the Combatting Autism Act, there was a committee created, or there was the statement

that there should be a committee created to plan how NIH and the other agencies in the federal government would allocate funding, not specifically for grants, but to set priorities in terms of research and federal funding.

So the federal government invited four scientists, as well as community members, people representing different kinds of practice and families, to create a committee to try to set these goals.

Q Were you appointed to that committee?

A Yes.

Q Now, your report also states that you are on the planning committee for autism and related diagnoses for the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders V, is that correct?

A That's right.

Q Is that also known as the DSM?

A Yes.

Q And is that an appointed position?

A Yes.

Q How many people are working on that planning committee?

A On the committee that I am a member of, there's probably 12. I think there are 12 different

people.

Q And what does working on that planning committee entail?

A Conference calls and meetings. But the goal is to try to create the framework, and then test the framework that will be used for diagnoses of autism spectrum disorders and other developmental disorders in the next round of DSM-V, which is the organization that's used in the U.S. for billing for children, which obviously has a huge effect on health insurance and the ways in which kids are covered.

Q Were you also involved in the formulation of the DSM-IV?

A Yes.

Q In what capacity?

A I was a member of that committee. And then our group received funding from NIH and also the American Psychiatric Association to try to test out when we proposed criteria to see whether they would really work, and how well clinicians could use them.

Q Do you hold any teaching positions in your specialty? I believe you touched on that earlier.

A Yes. I teach at the University of Michigan.

Q Are you a full professor?

A Yes.

Q And what do you teach?

A I teach assessment. I teach, I run training workshops in diagnosis. I teach developmental psychopathology research design.

Q And who are you teaching?

A I'm teaching mostly graduate students, although I supervise undergraduates in practical placements with regard to autism and research.

Q And how long have you been teaching?

A My first teaching job was in 1976, so 32 years.

Q Do you also, do you give lectures to professional groups or organizations specifically about autism and autism spectrum disorders?

A Yes, I do.

Q To whom do you lecture?

A Oh, grand rounds at medical schools, conferences, parents' groups, professional groups that want training in diagnosis or information about longitudinal studies, sort of looking at outcome and how kids change over time.

Q And how often do you lecture?

A I try to not do it more than once a month, but it probably ends up being more like 20 times a year.

Q Do you lecture internationally, as well as domestically?

A Yes.

Q And you mentioned that you lecture to family groups. Do you devote time to family-based associations dealing with autism?

A Yes. I mean, I feel like for a long time I tried to work with family groups, because ultimately parents are the people who are most responsible for these kids. So in Michigan I work with a number of parent groups. I've also had a longstanding affiliation with a group, several groups in Chicago, but one group in particular that designs wraparound services as services after school for kids with autism and adults.

Q I'd like to talk about your clinical experience, your experience as a clinical psychologist over the past 30 years, specifically as it relates to autism spectrum disorders. Do you currently have a clinical practice?

A Yes.

Q Could you describe your practice?

A I usually see one myself, usually working with one other person and a child psychiatrist. I see one new child coming up for a diagnosis a week, which

is about a 10-hour assessment, plus a school visit.

And then I also supervise a clinic with another five PhDs and a speech pathologist and a social worker, and each of them often sees a couple of other new kids, as well as we follow up the kids that we've seen before.

Q And are you affiliated with the hospital?

A Yes.

Q Which one?

A University of Michigan.

Q You mentioned that you diagnose and currently treat children with autism?

A Yes.

Q And you say approximately one per week?

A That's right. I probably see -- I might see five new kids a week, because I see kids that other people are seeing as their primary assessment, too. But I do the primary work for one child.

Q If you were to approximate how many children you've diagnosed with autism throughout the course of your career, what would be the number?

A I think the number I came up with was about 4,000, when you count kids not only that I've seen, done all the work for, but where I've supervised other people in the work and actually met the child.

Q Does that also include part of your research?

A Yes.

Q You're diagnosing children with autism. Are you currently following adults, as well, who have autism?

A Yes.

Q When you see a child with autism, do you follow him or her into adolescence?

A Yes. Our goal when we do assessments is to be available to follow that child, you know, or adult, as long as we can be helpful. So we have adult services in our clinic, and I still know adults that I met when they were two.

Q What are the age ranges of your patients currently?

A Right now we have a toddler clinic which goes down to 12 months, although most of the kids aren't really that little; and all the way up through, we have adult social groups and adult treatment programs that go up. We have a 50-year-old and actually a 56-year-old.

Q And do you meet with parents also as part of your clinical practice?

A Yes. I mean, parents are involved every

step of the way.

Q In what capacity?

A So we, part of our diagnosis is talking to parents about what their child is like at home and also in other circumstances. How their child has changed, what the parents have done, what the parents are worried about, trying to figure out what we can help, and also so that we're not making recommendations that just tell parents to do things that they've already done.

So we do almost everything that we do, unless an adult with autism prefers not to have their parents there, we do it either with parents right in the room with us or parents watching through an observation room.

Q Do you also have a research practice?

A Yes.

Q Could you please describe your practice? Your research practice.

A We have a number of major research projects going on at the time. We're involved in two early intervention projects, where the idea is to identify children as young as possible who are at high risk for autism. And one is a very, is a sort of low-intensity intervention, where parents do most of the work, and

we're trying to support parents and teach them things that will be helpful.

Another is a much more high-intensity intervention, where we provide people that go into the home and do 20 hours a week of work with these very small children. Both of these are randomized controlled trials, so there's a community alternative. And then we've developed something just so families don't get nothing who are not randomized into the main treatment, which involves parent education and a toddler group.

We also have a longitudinal study, where we follow children who are referred at age two for possible autism. There are two groups of kids: a group in North Carolina, which I saw when I was there, and a group in Chicago, which I saw when I was there. We've followed those kids, they are now 16 to 19 years old. And so we are actually just preparing to see them again. We saw them at two, three, five, and nine, and then have had parents on the phone and filling out forms for us every three months in the meantime, while we tried to get money to see the kids.

We're involved in the development of an instrument that will measure a spontaneous communication. There are a lot of tests that measure

vocabulary and children's ability to name things, but not, not a lot of good ways to look at how well kids could actually communicate. So we're trying to build on the diagnostic measures that we've created to do that in our moving through the development of an instrument to do that.

We have, we are the leaders of a big genetics consortium. Even though I'm not a geneticist, but my job is really to help the geneticist define what is autism; figure out ways that we can quantify different aspects of autism. That is, figure out how severe a social deficit is, how severe a language deficit is, and have that information available to researchers -- I mean, this is a public repository, so researchers will be able to apply to get access to this, to do studies of different genetic hypotheses, but also recruiting families into this program.

So that as we find things, not just genetic, we can go back and ask families, you know, do you want to be part of this neuroimaging study, because there is a finding that might be relevant to your child.

I think those are the main -- and we've just completed development of a toddler module, where we are trying to figure out if we can diagnose autism in

children as young as 12 to 18 months. How would you do it, you know, how can you convey this and teach other people to do this, given all the limitations and concerns about overdiagnosing little kids.

Q How long have you been researching autism?

A I started working in an autism research project as an undergraduate, so in 1969. And then, in graduate school, did other things, and then circled back to autism when I was in North Carolina.

So it's been, you know, if you count undergraduate, it's almost 40 years.

Q As part of your research practice, do you research the phenomenon of regression in autism?

A Yes.

Q And how long have you been researching regression in autism?

A We have been keeping track and trying to, in a very gross way, define regression since we began to develop the standardized diagnostic instruments. So that occurred in the early eighties.

And then I think I became more interested with what, what does this mean, and also more concerned that sometimes people were implying that regression didn't exist. And so I began trying to organize various groups that I was involved in to try

to get enough subjects so that we could actually look at whether we can answer, is regression a figment of parents' imagination, which I don't think it is. And then how can we better understand it.

So I was involved in a series of relatively large, some small-scale and then larger-scale studies, looking at the prevalence of regression. And then most recently we've been studying these very young children who are either siblings of children with autism, or whom somebody has a reason to think that they might have high risk for having autism, down to, you know, infants. And one of the reasons we did that was because we were interested in whether, if we saw kids regularly at very young ages, we might actually see the regression occurring, and would have a better sense of what was actually happening.

Q And how often are you seeing these children?

A Once a month.

Q And how long has that research been ongoing?

A That study has been going on now I think for about three years.

Q You had mentioned that you are one of the authors of the autism diagnostic interview, is that correct?

A Yes.

Q Is the acronym ADIR?
A Uh-huh.
Q What does the R stand for? Revised?
A Revised.
Q Who are the other authors on that?
A Michael Rutter and Ann Le Couteur.
Q And could you describe what that is and how it's used?
A The ADIR is a long, semi-structured interview, which means that rather than asking people yes-no questions, you ask the caregivers, usually parents, to describe specific contexts in which they have observed their child.

So the idea is that you really use the parents' knowledge as a window into looking for specific behaviors in children. And then the examiner uses that information to try to apply what the parents have said to specific criteria that would say yes, this child, for example, has difficulties in eye contact, or this child has unusual facial expression.

So rather than asking a parent does your child have unusual facial expressions, the idea is to get the parent to talk about facial expressions, and then to actually code that information.

Q And who uses the ADIR?

A The ADIR is used around the world, primarily in research. It's been translated into more than 20 different languages, and is used in I think tertiary care clinics, university clinics primarily, as well as in research projects.

Q And when was it first published?

A Oh, dear. It was first published in, the first one in 1989, I believe. And then we revised it and published the revised version in 1994.

Q And you're also one of the authors of the Autism Diagnostic Observation Schedule? Is that also referred to as ADOS?

A Yes.

Q Is that correct? Who are the other authors of ADOS?

A Michael Rutter, Pamela DiLavore, who is a special educator from North Carolina, and Susan Risi, who is another clinical psychologist.

Q And what is ADOS?

A The ADOS is a companion instrument to the ADIR, but which has actually been used, because it's shorter and fits a particular clinic need, it's now used independently, as well. It's a standardized observation, so the idea is that the clinician works with a child or an adult for about 45 minutes,

carrying out a standard series of activities. Different activities are available for different ages of kids, and also different language levels. So you do different things if the child can talk very well than if the child can't talk at all, or you do things, different things with an adult than a teenager or a child.

And the idea is that you create contexts for different kinds of social behavior. That is, by putting the situation in -- the child in a situation where they would likely want to request that you do something again, like blow bubbles. And then you look at how the child responds.

And because it's standardized, you can then compare how do typical kids do this, how do children with intellectual disabilities who don't have autism do this, how do children with autism or autism spectrum disorders respond in each particular situation.

Q And who uses the ADOS?

A It's used around the world by actually people from all kinds of disciplines.

Q Primarily for research? Or is it also used in the clinic?

A It's used a lot clinically, as well as for

research.

Q And have you authored any other diagnostic instruments?

A I was also involved in creating the screening instrument which is based on the ADIR, which is a series of questions really taken from the ADIR, but modified slightly, with the idea of having, you know, a two-page form that parents could fill out that would allow you to screen for autism.

And then I've also worked with a speech pathologist who's a collaborator in our very early intervention studies, looking at ways to define autism from coding videotapes of a general communication screening that she's developed.

Q And you've published over 125 articles related to child development and psychology? Does that sound about right?

A Yes.

Q Are they all peer-reviewed?

A I think those are, yes.

Q And do the majority of them pertain to autism spectrum disorders?

A Yes.

Q Have you published specifically on regressive autism?

A Yes.

Q In what way?

A We've done a number of different papers about regression, looking at the different samples that we were studying, both the longitudinal sample, the kids from North Carolina and Chicago, and then also trying to pull together data from various collaborations to try to look at regression.

Q How long have you been looking at regression?

A I think that we first started looking at it in the early longitudinal study. So that would have been around 1991, 1992.

Q According to your CV, you've published nine books. Is that accurate?

A Yes.

Q And you've published 61 book chapters in other publications that pertain to child psychology, including autism spectrum disorders, is that correct?

A That's right.

Q And you currently serve on the editorial board of six child psychology and autism-related journals, is that correct?

A Yes.

Q And what does it mean to be on the editorial

advisory board?

A It means that you agree to review a lot of papers, that you agree to review a paper at least once a month for a journal. That you're identified as somebody who is a specialist in certain areas. So that if there are general discussions about where the journal is going next, or conflicts, you will help sort them out.

Q And the journals on which you serve, are they well known in the field?

A Yes.

Q Could you name a few?

A Journal of Autism and Developmental Disorders, Journal of Child Psychology and Psychiatry, Child Development, American Journal of Mental Retardation.

Q And are you a reviewer for any journals?

A Yes.

Q A lot?

A Lots.

Q Have you ever testified before in a court of law?

A Yes.

Q How many times?

A I think three times.

Q And could you describe the cases?

A I testified twice in cases involving parents accused, through facilitated communication, of abusing their children. So I testified in order to try to sort out the validity of these accusations, working with families.

And then I testified in a case, in a case where a family was suing the state to try to get better services.

Q And why did you agree to testify for the U.S. Government here today?

A I felt like this is such an important question. And my expertise is limited in the sense that I'm an expert on behavior and development in autism and regression, but that is something that I've been working on for years. So I felt that it was important, since I was asked to come forward and be able to describe this, because so much time and energy and concern has gone into questions of the relationship between vaccines and autism.

Q Do parents in your clinic come to you with questions about vaccines and autism?

A Almost every day.

Q And what do you tell them?

A I tell them that at this point there is no

evidence that vaccines cause autism. And so they need to really consider the fact that, although it's very, that everyone wants to find a cause, and that's a very emotional need, that at this point no one has been able to find any clear evidence that vaccines contribute to autism.

Q Now, before we get into a discussion of regression, you had mentioned that you conduct longitudinal studies. What is a longitudinal study?

A A longitudinal study is a study that follows individuals over time. So, as opposed to comparing a group of two-year-olds and then a different group of five-year-olds and a different group of nine-year-olds, a longitudinal study would identify children, or it could be adults, at a particular age, and then follow those same adults over time. So that you can actually look at their development rather than make interpretations about development from polling different people and comparing them because they happen to be different ages.

Q And how long does such a study usually last?

A Well, it's difficult to do them, because the way that funding works, at least in the federal government, is you tend to get five-year grants. But I think that, you know, there are longitudinal studies

in autism, and ours is probably the longest, where we follow the kids now for 17 years.

Our study of the toddlers has gone on for three years, and we hope we'll be able to follow those same kids longer.

Q Now, on page 2 of your report you state that, "Changes in behaviors associated with autism over time are predictable according to children's language level, social deficits, and the frequency and severity of their repetitive behaviors, as well as their parents' involvement in behavioral treatment."

Could you just further explain what you mean by that statement?

A That's a statement based on our longitudinal work. And what we did here was look at what were the characteristics of children at age two and at age three and at age five, and look at things such as how much language did they have at two, how much repetitive behavior did they have. Judge both by our observations using the ADOS, and also by their parent reports on the ADI, and then also on other measures.

And then what we tried to do was predict what would the children be like at age nine. And most of the analyses have consisted of saying do the children still have autism, do they have classic

autism, do they fall within the general area of autism spectrum disorders, PDDNOS, or you could say Asperger's Syndrome. And then also how well are they functioning, what's their language like, what's their nonverbal, what are their nonverbal skills like at age nine.

And so we were able to say, to find particular factors that, when you looked at those factors, allowed you to make more accurate statements than if you just randomly guessed which children would still have autism, which children would fall within the realm of PDDNOS or have milder characteristics, on the basis of those, those features.

Q Dr. Lord, I'd like to now turn to a discussion of regression in autism. Does regression in autism exist?

A Absolutely.

Q What is regression in autism?

A Regression in autism is the phenomenon of children who have some skills that are observable and documentable over a period of time, who then don't produce those skills, either stop producing them or produce them on much less frequency.

This is, in autism, because of the way that autism has been defined, these regressions have

typically occurred in the second year of life, maybe the end of the first year of life.

So in autism, typically we have not addressed later losses, for example, somebody changing during adolescence, but focus on those really early years. But there is quite a lot of research looking at this, these changes in these very early years.

Q And is regression confined just to autistic disorder proper? Or is it found within any of the other spectrum disorders?

A There are other disorders that are -- and certainly other spectrum disorders. And so in our research we found that regression occurred both in children with classic autism, and also children with PDDNOS or milder phenomenon.

Q Is regression a new phenomenon?

A No. Regression was first described many years ago, even by Leo Kanner.

Q When was it first described in the literature? Back in the forties?

A Yes.

Q And how was it described back then?

A The first ways in which regression was described, people tended to focus on the fact that children were described by their parents as having

normal development, and then losing skills. So I think those initial descriptions focused on that normal development, which I think now we don't think is the case, and probably isn't the essence of regression.

But I think that partly came from the fact that this was a new idea, and people were just noticing that there was an unusual pattern here.

Q How is regression assessed by a clinician? Or a researcher?

A The most typical way is by very careful interview of parents. So I think that their, because their regression involves two things -- it involves having skills, and then losing them -- you have to have very specific information about the skills that the child has in order to document what they've lost.

And because there's huge variability even in that, you know, narrow time period, say, between 12 and 18 or 12 and 24 months, as to how many skills kids with autism spectrum disorders have, you need to very carefully determine what they could do, when they could do it, how specific those skills were, and then figure out what they can't do any more.

And then, because many children start getting back some of those skills, you have to figure

out where you are in that continuum. You know, are you at a point where the child is losing skills, is relatively stable, or gaining skills? That also differs across skills.

So I think the primary method is a very detailed parent interview.

Q And are there certain particular questions that must be asked of the parents?

A Right. If you don't ask parents specific information, you often won't get it. Because parents are filled with information, but often don't know what's relevant, or don't know what you're thinking about.

Q Does it also depend on how the question is asked, how it's phrased to the parent?

A Absolutely.

Q And what skills are typically lost in regression?

A We used to think that the primary way that we should define regression was loss of words. But it's become apparent, through the research that we've done and a number of other people have done, that what's most common are the loss of social skills.

And in fact, in our study of toddlers right now, we've found that the majority of children who

develop autism actually lose social skills. So in fact, if you define regression by loss of social skills, almost all children with autism show a pretty marked documentable loss of certain social skills, such as eye contact, attending to people, engaging in social interaction in the course of that second year of life, from 12 months to 24 months.

Q What are the skills that are typically first recognized by parents as a sign of regression?

A Kids who stop talking. Kids who may have had social routines, like peek-a-boo or waving or going "so big," who stop doing that. Kids seeking their parents out, so wanting to find people to play with or to be engaged in. Smiling, sort of general positive affect. Understanding sort of little jokes. I mean, not being able to catch a child's eye and make a face at them, and have them respond.

Q Now, in your report you say regressions in autism follow a predictable pattern. Could you explain what you mean by that?

A The point there is not that all children are the same, but there does seem to be a pattern in which children, children are acquiring skills, and then this acquisition slows down. So that the sort of prototypical example would be a child who at 12 months

says mama, dada, baby, maybe the name of their sister.

And if you go through a list with the parent retroactively of here's 25 things that most 12-month-olds can do, that child may not do all 25 things. I mean, actually probably nobody does all 25 things. But they might do 18 of those things.

And then what happens is that the child doesn't progress. So they may have those few words, but for months they don't acquire new words. And perhaps those words begin to appear less frequently.

Then there comes a time where the child stops talking completely, or will only say mama, but doesn't say those other words. And at the same time has become socially less engaged, so may spend more time by themselves. May develop odd behaviors, may become attached to a banana peel or suddenly want to do sticks, or become fascinated with buttons on the television.

So you have this combination of having skills, you know, and being on a trajectory of developing things; slowing down for a while, not seeming to acquire many more skills; and then some of those skills just sort of fading out.

The trouble is that also at the same time, the child may be developing some other good skills.

So in our study where we're watching kids every month, we need to be able to see that at the same time some things are getting worse, often other things are getting better.

And you know, the children are not on timers. So it's not like everyone does something at 12 months, 13 months, 14 months. You may have some children who slow down at 13 months, and then start developing, you know, good skills at 15 months; and other kids who are still slowing down at 14 months.

So the trajectories are similar. That is, you can literally draw lines that look quite similar, but they're spaced out, and the timing is shifts. You know, not in a huge amount, but definitely over a six- to eight-month period.

Q Are all regressions the same?

A No. I mean -- because partly you're talking about in order to define a regression, you can only lose what you've already got.

So a lot of this depends on what was the child able to do before this process started, where they slow down and begin to lose skills. And there's huge variability.

There are some kids with autism who never wave goodbye, you know, or don't wave goodbye in the

first two years of life, just don't don't figure out how to do that. So they can't lose it. Other kids who may learn how to do this, and lose it. Other kids who may learn how to wave, and keep waving, but may stop talking.

So it's almost like you have this constellation of skills -- again, that list of, you know, 25 things -- and there are similar patterns, but nobody is exactly the same. The timing is different, and the specific skills vary considerably in terms of which of those are lost, in part because they vary which of them are gained.

Q Do autistic children who have regression typically lose motor skills, as well?

A No.

Q What about autistic children in general? Do they lose motor skills?

A Not very often.

Q What has research shown to be the main component of regression in autism?

A The main component of regression is loss of social communication. So I think that we had initially focused on word loss, because it's much more reliably reported. That is if you ask parents years later what happened in your child's early development,

you know, mothers and fathers agree with each other more about loss of words than they do about social skills.

But I think that when we've had detailed studies that have asked more carefully about social communication skills, it's apparent that there are more kids who lose social skills than there are who lose words. And that that loss of social skills is probably, in the long run, more characteristics of autism than just word loss.

Q And is regression a gradual process, or a precipitous process? Is it an either/or?

A Yes, it's not an either/or. Because I think, think its as I said, we're talking about a moving target. I mean, loss of skills, loss of social skills is more the norm in autism than the exception.

So if we describe kids as having a regression who stop, who go from looking at people to some degree when they're nine months old, to looking at people less often by the time they're 15 month-olds, then probably almost all children with autism would have a regression.

If we set our threshold higher and say you can't have a regression unless you've had 20 of those social skills and lost 15 of them, then we get a much

smaller number.

Q Has your research found that regression is always characterized by a very clear decline or loss of skills?

A No.

Q Do children who lose words as part of their autistic regression ever regain language?

A Yes, most of them do.

Q What language level do they typically reach?

A Well, our research suggests that the language levels that the kids who have regression reach are very similar to kids who haven't had regression. There seems like, in our study, there is a slight downward skewing; that is, the kids who have had regressions come out with about a 10-point lower score in verbal IQ when you look at them years later than kids who didn't have a regression.

One other study found the same thing we did, and several other studies have found no difference.

Q Is there a typical duration of time between word loss and regaining language skills?

A No. There's a huge, there's a huge variability. And that's another important aspect in the definition of regression, is how long do you have to have lost skills before you officially have a

regression.

When we interviewed parents of two-year-olds, we found kids who had lost skills for a month, and then started regaining them, as well as kids who stopped talking and actually never talked again, or started talking months later or years later. So there is a huge range. And that probably also confounds trying to figure out what regression is, because parents have different memories about a child who didn't talk for a month than a child who had five words, and then never spoke again.

Q Do children with autism in general improve?

A Absolutely.

Q What percentage, do you know?

A I mean, I think all children with autism improve in some ways, and how much is highly variable.

Q Would that include children who have a regression in autism? Do they improve, as well?

A Yes.

Q Do we know why?

A No. I mean, some of the improvement seems to be getting back on developmental course. I mean, it's like asking why do normal kids learn to do the things that they do or why --. We can describe how they learn things, but that process of, you know, how

do kids learn to walk or talk when no one is really teaching them, we don't know. And that's the same for autism.

We know that, you know, behavioral treatments make some difference. But it's a relatively small amount of difference compared to just that force of development.

Q You talked about the majority of children who have suffered a loss of words, regain some level of language. Do they also improve in their social skills?

A Yes. I mean, not as, not -- with language you have some children who regain language and are as fluent as any of the rest of us. Not a huge number, but that definitely happens.

In social development it would be very rare for a child to not have some kind of residual social deficit, but that also happens with kids who have regressions or kids who didn't, in a very small portion of kids with autism.

Q Is autism in general associated with any particular ethnic group?

A No.

Q What about regressive autism? Any particular ethnic group association?

A No.

Q Is regressive autism associated with any particular social class?

A No.

Q Any particular gender?

A No.

Q Any particular birth order?

A No.

Q If an autistic child has regression and lost skills, does that mean that the child was developing entirely typically before the regression?

A No. I mean, I think that's one of the most important things that the research has figured out. That just because you have a loss doesn't mean that things were normal to begin with. They're actually different factors.

They're not independent, because obviously you can't have a loss if you didn't have some skills. So a child who was developing very, very slowly and had very limited skills would be less likely to have a loss because they don't have as many skills to lose.

But given that most children had some skills, the presence of a loss does not mean that things were normal to begin with. And it's very clear, from many research studies in the last 10

years, that most children who have losses showed deficits prior to that loss. So the loss does not, is not an indication of normality or abnormality; it's a separate question.

Q Have you ever heard of the term "clearly regressive autism?"

A No.

Q Is that term discussed in the published literature anywhere?

A Not that I know of.

Q Doctor, is there a distinct phenotype among people with autism who had completely normal development during the first year of life, and then suffer a regression in the second year of life?

A I don't think so.

Q Is a review of pediatric records during the first year of life a reliable way to assess whether or not that child was developing entirely typically during that time period?

A No. I mean, if you had a pediatric record that indicated concerns, you would certainly take that seriously. But to have a pediatric record that doesn't mention anything, you have no idea if the pediatrician didn't ask, if the parents said something and the pediatrician didn't happen to record it, or if

the parent raised a concern and the pediatrician ignored it.

So the absence of information, the absence of abnormality in a pediatric record, without very systematic questioning, means nothing.

Q Are pediatricians usually attuned to subtle abnormalities that later manifest as autism?

A They are getting better, but in the past that has been a major complaint of parents, is that pediatricians don't necessarily see or take seriously the kinds of difficulties that their children have.

Q Are parental accounts of typical development during the first year of life an accurate measure of a child's development during that time?

A I think parents' accounts are the best source of information we have. I mean, with the advent of videos, we also have videos, which made a huge difference, as well. But people don't necessarily video their children in all sorts of situations, and they don't do it systematically. They don't say I'm going to always video my child, you know, every Monday taking a bath, and every Tuesday eating a meal.

So I think parents, parents are our primary source of information. The problem is that what you

get depends on what you ask. And it also, parent reports are affected by memory. So you will get quite different reports sometimes if you ask parents of six-year-olds versus asking parents of two-year-olds what they are, so that they're not, they are flawed, but I think they are our best source of information.

Q Doctor, I'd like to turn our attention to the Richler study, which is filed as Respondent's Master List 397. Are you familiar with this study?

A Yes.

Q Were you one of the authors of this study?

A Yes.

Q What was your responsibility with regard to this study?

A I was the PI for carrying out this study, and I supervised --

Q What's a PI?

A Sorry. Principal investigator. So I was responsible for this study. And the person who was first author, who did the initial draft, was a graduate student of mine, and I worked with her to gather the data, analyze the data, and write up the interpretation.

Q And what did this study investigate?

A This study looked at whether we could find a

clear regressive unit type of autism. That is, we were trying to take descriptions that had come out of previous research, and see if there was some validity to them, and whether this phenotype was related to the MMR vaccination.

Q And how long did this study take to compile?

A The study used existing data, so that we took data from a number of sites around the country that were all involved in different research projects, but we all decided to use the same methods to diagnose autism and to describe the children with autism. So those studies had been going on for about five years.

And then we took existing data, cleaned it up, which took about a year, and then did followup interviews and organized the other sites to do followup interviews of children identified in that dataset. That probably took another two years. And then analyzed the data and wrote it up.

Q And how did you investigate whether regression is the distinct phenotype within autism?

A What we did was try to take the major principles that people have used to define, to suggest that there are, that there is a special group of children with autism who have regression; and that those children are different from other children with

autism.

And at the time we really started with the hypothesis that they were different, and that we wanted to see how they were different. And so what we did was define regression. So in that study we defined regression by having a loss of words. But then we also had very systematic questions about loss of social development.

And it turned out, over the course of this study, that children who lost social skills were not different from children who lost words and social skills; and that almost all the children who lost words also lost social skills.

We then looked at various aspects of those children's development in terms of their acquisition of the social skills before the loss, and compared them to typically developing children. And then we looked at different characteristics, such as the existence of GI symptoms and things like gender, ethnicity, birth order, to see if there was something special about those kids who had had these losses.

Q And did you find any differences?

A We did not find much. We found minor differences in the outcome, in terms of verbal IQ. That is, the children who had a regression were

slightly lower, about 10 points, which is a real difference, but not huge, at later ages. And we found a slightly higher frequency of parents' reports of diarrhea and constipation in the children who had had regressions.

Q You said that you started with the hypothesis that there was a difference between regression and nonregression. Why did you start with that hypothesis?

A Well, I think we had heard about regression for years from parents that we worked with. We had seen children, especially siblings of children, so we would know a child with autism, and then meet a sibling who people thought was typical, and then watched that child become autistic. So I think we were starting from the point of view that we wanted to be sure that people didn't dismiss regression as if it didn't exist.

And then, I mean, regression is a very striking phenomenon. To watch a child gradually become autistic is a heartbreaking situation, and something that's very hard to forget. So we were interested in what does this mean. And also a question of it this, are the children who experience this different in some way from children who don't.

What we found out is that there isn't a cut-and-dried regression/nonregression. There are these continuae of changes, most -- some of which seem to happen for almost all children with autism, and some of which don't. And the more we looked, the less we found that was very clear.

Q What did you find with regard to the regressive group's development before they had a loss of skills?

A We found that most of the children who were identified as having regression, when you went through parents and asked them could your children do this, this, this, this prior to age two, were actually behind before their regression had occurred.

Q Were there children who appeared to have near-typical development prior to the loss of skills?

A There were children whose parents reported that they had more skills. So that if you just added up the number of these different social skills, there were children who had regressions, who had the same number of social skills as a typical child.

Q Did those children fit the lower IQ, the diarrhea profile that you found, with the other children who had a loss?

A No, they didn't. So we didn't find any

clustering of the characteristics that people had suggested might define this regressive subtype. As we found, we did find minor differences in GI. We did find that there were kids who lost, who had more skills, but we didn't find that they went together.

Q Now, you mentioned that this study also considered whether autistic regression was associated with the MMR vaccine?

A That's right.

Q And what did you conclude?

A We could not find any relationship between the regressive, between regression -- or when we defined this group and said well, if there is a regressive phenotype, this is who other researchers would have said would be in it. We couldn't find any relationship between that and having an MMR vaccine.

Q Doctor, does the Richler study support the notion that there is a distinct phenotype in autism known as regressive autism?

A No.

Q Had you ever heard the term "regressive autism" back when you were first looking at the phenomenon?

A I think my first exposure to the term "regressive autism" was as it was applied to the work

of Andrew Wakefield and the MMR vaccine.

Q Before that work, how was it described or considered by the autistic community?

A Before that, I think that most people, most researchers felt like regression is one variable in looking at early development.

Q Does any of your research or research of others support a distinct subtype of regressive autism?

A No. I mean, I think especially as we've looked at the toddlers, it becomes, you know, as we look at the toddlers it's clear that even these very large studies, where we felt like we were asking parents many, many questions in great detail, probably do not get at the essence of what happens in those early months. Because the changes are more subtle, and our ability to observe them is so much dependent on the context. It's dependent on when do you see a child and what are you looking for.

So I think that that has moved us, and I think much of the field, toward a sense that there isn't a regression or not a regression; there's the question is the degree and type of worsening that occurs, how long it lasts, and how much, how many skills a child has before that occurs.

Q Now, in terms of the clinical outcome of a five- or six-year-old with autism, is there any marked difference in the clinical outcome of a child who had what I'll term early onset autism, versus a child who did indeed have regression?

A Most studies have found no difference at all. The studies that have found differences have found these relatively small differences in verbal skills.

Q You touched on earlier, Doctor, that you are continuing to research the phenomenon of regression? Is that correct?

A That's right.

Q And you're conducting a longitudinal study, is that correct?

A That's right.

Q And what information is emerging from that study with regard to regression?

A With that study what we've been doing is seeing children who are at risk for having autism either because they have a sibling with autism, so they may not have any behaviors associated with autism, but they have a sibling, and their parents are eager to have somebody follow them -- or something has occurred, or something has been seen, often identified

by parents, but sometimes by physicians, pediatricians. For example, the child has had seizures in the first year of life, and so someone is concerned that this child might develop autism.

And we see the children once a month, have parents fill out the same forms each month. And then we do a standardized assessment, a toddler version of the ADOS. So we do a standardized observation of the child's social behavior with us and with the parents every month.

What has come out of this is that the trajectories are much less clear than we would have thought from retrospective descriptions years later of what the children are like. And when we have tried to sort that out, I think that there are a number of implications.

One is that different skills are changing at different rates and at different times. So that you have, for example eye contact is typically getting worse for almost all of the children from 12 months to 24 months. So that, and social engagement, responsiveness to somebody trying to get the child to interact with them, both us and the parents, typically is getting worse in children who have autism diagnoses say by the time they're two and a half.

So those things are changing, but they actually cycle back around. So they get worse for a while, and then for some children they start getting better again.

We also have other skills. For example, a response to attention or response to somebody pointing, or trying to get the child to look at something. And that, for a number of kids, gradually gets better, even at the same time that some of these social skills are getting worse.

So I think what we've realized is that this is, it's just much more complicated changes in development than we thought. And that these things that we used to think only happened in kids who had regressions are actually happening in almost everybody who has autism.

Because there are some children who look very different from typical children at 12 months. But those are few and far between. And in fact, in our followup study, that isn't necessarily predicted. The kids who are not making eye contact at 12 months are not the most autistic kids at age three.

So many things change during that toddler period. And I think that our conceptualizations of what regression is are partly based on retroactive

trying to figure out what happened and didn't happen, which is quite different than when we can see it happening right before our very eyes.

Q Doctor, are you aware of any evidence showing that the etiology of regression in autism is different than that from nonregression, for lack of a better word?

A No. And I think again that the idea that there aren't these clear patterns makes it much harder to draw conclusions about etiology. Because basically, you could arbitrarily divide these kids up in millions of different ways.

So far, no matter -- people have tried to divide them up, and haven't found any differences in etiology. But it's not even clear that, that we know how to divide them up, or they can be divided up.

Q Doctor, before this litigation, had you ever read in any published literature that thimerosal-containing vaccines caused regressive autism only?

A I had not.

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

A No.

Q Doctor, did you review the report submitted by Dr. Marcel Kinsbourne in this litigation?

A Yes.

Q On page 14 of his report, he states that, "The late onset of the regressive subtype and the subsequent remission or relapses become more understandable if autism is due to disease than if it is the aftermath of congenital maldevelopment."

Do you agree with this statement?

A No.

Q Why not?

A There are many different disorders where onset occurs later on. I mean, we have Huntington's disease and schizophrenia and sickle-cell anemia, and all kinds of disorders that children, where, where we in some cases we know are genetic, but which occur later on. So I think we can't make a simple inference that because something emerges later, that means that somehow someone has caught a disease or had some kind of particular environmental event that caused it.

Q And Dr. Kinsbourne also draws a distinction between what he terms as classical or congenital autism, and regressive autism. Is this a proper distinction?

A I think the term "congenital autism" means nothing. Because, I mean, as I said, it's a developmental process. We can't diagnose autism in a

brand-new baby.

And so in all cases, something is developing that would lead us into autism. So to make this distinction between congenital and regressive is a false dichotomy.

Q Now he's also -- And Dr. Kinsbourne has also described what he terms his overarousal model as an explanation for autistic behavior. Does his overarousal model accurately describe what is known about autistic behavior?

A I don't believe so. I mean, the overarousal model has been around for 40 or 50 years, and used to described many different disorders.

I think one of the hard things is that it becomes very circular. I mean, children with autism do respond to being overstimulated, as do many other kids. And children with autism may respond in more conspicuous ways, and may have a lower threshold.

But the problem is that often the behaviors that are used to say that a child is responding by overarousal -- for example, Self you know, flapping or getting very physically excited or distracted -- are the same behaviors that occur when a child is underaroused.

You know, we can get children who have a lot

of self-stimulatory behaviors, you know to do these behaviors by putting them in a situation where there's nothing to do. We also see children do those behaviors when they're very happy, or when they're not so happy.

So the behaviors that are used to define overarousal are behaviors that occur in many different contexts.

MS. RICCIARDELLA: Thank you. That's all I have.

SPECIAL MASTER VOWELL: Are you prepared to proceed?

MR. POWERS: Yes, I am. Good morning, Dr. Lord. Go ahead and refill the water there.

CROSS-EXAMINATION

BY MR. POWERS:

Q My name is Tom Powers, along with Mr. Williams at the table with me. We represent the two families here, as well as the Petitioners' Steering Committee.

I do have some questions to ask you, as you might imagine, based on the report that you filed and the testimony you gave today.

Your testimony, as I understand it, and your opinion is that there is no phenotype for regressive

autism. Or perhaps a more specific way to put that is that regression in autism is not a distinct phenotype within autism spectrum disorder, is that correct?

A Yes.

Q You've also described regression in autistic children as a striking phenomenon. Do you remember that testimony?

A Yes.

Q What is the difference between a phenotype and a striking phenomenon? How would you describe the difference between phenotype and striking phenomenon?

A My point about the striking phenomenon is that it is, it is a remarkable experience to watch a child who has been able to do things, not be able to do those things. Or to watch a child who has been relatively socially engaged become less engaged, and be more and more difficult to engage or attract.

But I think that is different than a phenotype. Because a phenotype implies that there are a cluster of behaviors that are associated with each other. And that there is something unique about that cluster of behaviors.

I think regression is a real phenomenon in autism, but there is a continuum of regression. It's not -- and we can create a phenotype. I can say well,

I'm only putting kids who lost words into this group, and I'm going to call it the Lord phenotype. But there has been no, nobody has been able to show that that phenotype is associated with anything other than the characteristics which I used to define the phenotype.

Q And that would be because, as I understand it, autism diagnostically is entirely a symptomatic diagnosis; that is, there's not a biomarker, there's no underlying pathology that one would use typically, is that correct?

A It's not, the problems with defining the phenotype aren't because autism is defined purely by behavior. It's because we haven't been able to find an association between any of these particular phenotypes that people have pulled out, and the ways in which people have pulled out the phenotype.

Q Now, the autism diagnosis typically covers three domains. There's the communication skills, social reciprocity, and play and behavioral skills, is that correct?

A That's right.

Q I heard a significant amount of your testimony on direct focused on the social reciprocity and the communication domains. I didn't hear a lot of

discussion about the play.

In your work on regression, do you have an idea of what percentage of children who had regression, regressed in the area of play and appropriate play?

A That's a good question. There's probably less loss of play, because many children, at the time the losses occur, are not playing very much. I mean, it partly depends on how you define play.

If you define play in terms of social play, then in fact you do have regressions. And that would fall under what I was talking about before, like peek-a-boo and pattycake. I mean, those aspects of play.

If you're talking about play as using toys or using materials, that, when you're looking at a 15-month-old with autism, many children are not play-using materials in a terribly useful way. So there's less loss than you would see in the other areas.

Q And that actually is the type of play that I was, that my question was designed to get to. Not sort of the social reciprocity play, but using toys appropriately. So if you have tools, you actually use them as tools; or if you have trains, you actually use them as trains.

In thinking of that kind of play, are you

aware of any studies that demonstrate children who reached a point where they were playing with toys in a functionally appropriate way, who then lost those skills, and played with those same toys in nontypical ways?

A I'm trying to remember. In our studies of the toddlers, we do document changes in play. What we do see is an increasing amount over this period of time of nonfunctional play.

So I think one of the things we really don't know is the degree to which is the child, a child who might be losing sort of imaginative play, versus gaining repetitive behaviors that are more attractive to them.

So if you think about a child who has got a car and they are pushing it back and forth, a parent may think, and we would probably think the same thing, that they're doing something imaginative if you start with that. What is more typical of the changes over time is that a child may move from moving that car a little bit, to then wanting to line up a number of different cars. And that is typical actually of children that we've seen, both who have had losses and who have not had losses.

Q Do you have a sense of sort of the larger

picture of things, what percentage of children in this area normal development preceding loss, I think is the descriptive phrase you used. If you look at the number of children who do have regression, what percentage of those children do you believe actually were normal, neurotypical, in the period of time preceding their loss?

A I don't think we can make a distinction. I mean, I don't think we can divide kids up as to normal and abnormal.

I think what we have to do is think about how many skills they had before the autism became apparent. And I think there are some kids who have quite a few social communication skills before autism became apparent, and other kids who had fewer.

But I don't think that it's probably of much value to try to say who is normal and who is not normal. Because we are making all these inferences retroactively. And some of it is going to depend on parent reporting how much parents knew, and the way in which the questions are asked.

Q And did you hear the testimony of Dr. Rust when he appeared?

A No.

Q Well, Dr. Rust described that within the

children that he sees, the ones that are reported to be regressive, he actively does this retrospective analysis and attempts to identify, earlier in time, earlier symptoms that might have been missed.

And he testified that in about 20 percent of his described regressive autistic patients, he cannot find anything abnormal in their early development. So that he described basically the answer as 20 percent.

Is that answer consistent with your experience, that perhaps 20 percent of children who regress, even retrospectively show no abnormal signs of early development?

A I don't know.

Q One of the issues in this litigation -- and as you're probably aware, is discussing the causes of autism now -- you would agree that genetics are a significant contributing factor to the development of autism?

A Yes.

Q And that heritability is something that is distinctive when one is evaluating the etiology of autism spectrum disorders.

A I think that we have to make a distinction between heritability and genetics. So it seems very likely that there are genetic components to autism;

that is, genetics contributes to your risk of having autism.

Whether the degree to which that's inherited, that is, that you actually, it's passed from family member to family member versus it's something that happens in very early points of conception which changes your genes, I think we don't know. I mean. Yeah.

Q Well, in a lot of the testimony we've heard, one of the big issues is this focus on genetic contributors and looking at concordance rates, particularly in twin studies. Are you familiar with the concordance studies involving both monozygotic and dizygotic twins?

A Yes.

Q And you would agree that the high concordance rates reported in those studies is evidence that there's a strong genetic component in autism, correct?

A Yes.

Q Now, in your report on page 3, you describe that regressions are not concordant within families, correct?

A That's right.

Q So if regression cases of autism are

nonconcordant within families, that would suggest something other than a heritability factor involved in the etiology of those cases, correct?

A I should be clear, that the paper that I was citing is a paper that was presented for a PhD dissertation, which has lately become quite controversial. So I'm not sure now what that means.

Q All I'm saying is you cited it in your report for the proposition that regressions are not concordant within families. That's what you cite it for.

A Right.

Q So are you saying now that you've changed your opinion on this issue since writing your report?

A Yes. I'm saying that I don't know; that I would not say that over again.

Q Is there anything else in your report that you would reconsider in light of recent evidence?

A I don't think so.

Q But if it's true that autism is not concordant among regressive cases, that would strongly suggest that there are other nongenetic factors involved, correct?

A Not necessarily. I think the point there was that regression isn't a yes-or-no phenomenon. I

mean, in fact, while autism spectrum disorders are concordant within twins -- that is, if you have one twin, the chances of an identical twin having something within the range of autism -- the narrow definition of autism is not concordant. So you can have twins, identical twins, where one child is very severely autistic and intellectually disabled and nonverbal, and another child who has very mild, subtle difficulties.

So whatever is concordant isn't this kind of autism or that kind of autism. So it wouldn't be surprising if the developmental pattern is not concordant, as well, since we know that things like IQ are not necessarily concordant within twins.

So it doesn't mean that it's not genetic. It just means that whatever is genetic about autism is a risk factor for this very broad kind of problem.

Q And it's a risk factor that makes one at risk for a whole host of nonheritable, nongenetic factors, correct?

A We don't know.

Q Well, if it's not heritable and genetic, it would have to be something else, correct? I'm not asking you to name what it is, but it simply would have to be something else, correct?

A But I guess I'm not saying I don't know if all of autism is hereditable. I think the question is, I mean it could be that it's not inherited by, it's not through a particular gene, but it's a combination of other genes that actually don't have anything to do with autism, except they affect the way that the child learns.

Q And they would affect, those various genetic permutations within an individual would affect the way that they respond to environmental stimuli, whether it's a learning experience or environmental exposures to substances, correct?

A We don't know.

Q I understand that we don't know, but that is one of the etiologies that one would have to look at in attempting to describe what caused a particular case of autism, correct?

A Yes.

Q Now, in your role sitting on this NIH strategic planning committee, did you participate in the 2007 IOM Environmental Factors in Autism Workshop?

A No. This committee didn't exist then.

Q So this committee was formed after that?

A Yes.

Q Is the committee that you're sitting on

currently evaluating any of the research suggestions or research proposals that were generated in that 2007 IOM meeting?

A The committee that I'm sitting on doesn't evaluate proposals. The committee that I'm sitting on just tries to look at what directions federal funding should take in the future.

Q Is one of the directions your committee is considering spending federal research dollars to look at potential environmental factors that influence the development of autism?

A Yes.

Q Are you involved with the NIEHS expert panel that was convened in 2006?

A No.

Q Are you, in the work that you're doing now, are you considering the NIEHS expert panel recommendations on additional research that could be done, particularly within the vaccine safety data link, to start explicating the various causes of autism? Are you involved in any of that work?

A The committee that I'm on is looking -- again, it's much broader. So it's not at a level at all of looking at specific proposals.

Q If not looking at specific proposals, are

you looking at general proposals coming out of that NIEHS workshop to look at environmental contributions to autism?

A We're not even looking at general proposals.

Q In describing the role of vaccines in autism, you describe the Richler study in some detail. That was a study that focused on the MMR, is that correct?

A That study was -- yes. I mean, yes.

Q Are there any other studies that are published right now that look, as far as you know, at an association between thimerosal-containing vaccines and the regressive features of autism? Specifically looking at regression.

A Not that I know of.

Q Are you aware of any that are ongoing, let alone published?

A There are, I am aware that there are studies on thimerosal. But that's the level of my familiarity.

Q The longitudinal study that you were working on, that you had some it sounded like anecdotal interim data, is that correct?

A That's right.

Q So the findings of the longitudinal study

have not yet been peer-reviewed?

A That's right.

Q Are they in the form of a manuscript that is about to be peer-reviewed or submitted for publication?

A Yes.

Q When do you anticipate that that's going to be submitted for peer review?

A Some time in the next couple months.

Q And upon submission, it would then be peer-reviewed; but up until now, this is sort of an anecdotal report on preliminary findings, correct?

A That's right.

Q Is this study NIH-funded?

A Parts of it, yes.

Q You have mentioned that in a large number of cases using this retrospective search, so to speak, for preregression normalcy, you said that the more you look, the more signs that one tends to see, is that correct?

A The more signs of --

Q Of nonnormal --

A Yes.

Q -- preregressive development. But you certainly don't see the lack of normalcy or latent

abnormalcy in all preregressive cases, correct?

A No.

MR. POWERS: I have no further questions.

SPECIAL MASTER VOWELL: Any redirect?

MS. RICCIARDELLA: A few.

REDIRECT EXAMINATION

BY MR. POWERS:

Q Dr. Lord, Mr. Powers asked you, spent a lot of time discussing genetics and autism. Are you a geneticist?

A No.

Q Do you claim to be?

A No.

Q He also asked you about the NIH committee that you sit on looking at environmental factors in autism?

A Yes. I mean, the NIH committee that I'm sitting on is looking at trying to set priorities for federal funding related to autism across practice, across -- well, across research that affects everything, from practice to looking for etiology.

Q He also asked you a bunch of questions about the type of play that is indicative of a loss. And you distinguished between playing with toys, as opposed to social play.

A Uh-huh.

Q Is this a way to define a phenotype?

A Many people describe play in autism as part of assessments. It turns out that using it as a way of defining a phenotype has not been very helpful, because there is such variability both between, or among kids with autism, but also typical kids.

So the reality is that most typical kids can use an object to pretend that it's something else by the time they are 18 months old. But whether they'll do that in any 45-minute interval, or the amount of time that they spend doing that, is hugely variable from kids who don't have a lot of imaginative play and spend much more time running around, or in social play in kids who are, you know, making toothbrushes into dolls from very early ages.

So it turns out that it's a very interesting phenomenon, but it hasn't been very useful in terms of defining phenotypes.

Q And is the change in the way one plays with toys a characteristic, the most characteristic loss or type of skill lost in regression?

A No.

Q Now you were asked a couple questions about the Richler study, and whether it focused on MMR. Was

that the only point of the study?

A No. The focus -- I mean, the point of the study that's written up in the Richler paper, which is also written up in several other papers, was to see if we could get consistent descriptions of regression across these, you know, 10 different sites around the country.

So it was really to say, you know, can we verify that regressions occurred, using standardized measures that where everyone is asking the families from these different research projects the same questions.

Q And Mr. Powers also referred to your ongoing longitudinal studies. And he termed your findings anecdotal.

Doctor, are you describing your findings in that study, in your opinions here today, are you basing those on anecdotal evidence, or on your experience?

A Well, it's not anecdotal evidence, in the sense that we have 50 children that who have autism spectrum disorders who we have followed in a very systematic way over the last three years. So I'm not just describing one child that I've seen; it's data that's been analyzed by a team of people. But what we

have not done yet is finalize a manuscript that's been sent off for peer review.

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER VOWELL: Recross?

MR. POWERS: A couple of just very quick questions.

RECROSS-EXAMINATION

BY MR. POWERS:

Q Doctor, in getting back to this issue that Ms. Ricciardella was talking about, the repetitive, the play areas and the different domains. Do you have a sense, what percentage of regressive cases demonstrate a loss of skills across all three developmental domains? Do you have an idea?

A Well, from the, let's see, from the toddler study, the study where we are following kids, there are different patterns across those areas of skill. And there are actually, even within an area there are different patterns.

So there are, so that certain losses of skill are very common, and others are much less common. Again partly because you can't lose a skill until you have it.

I don't have a sense of -- well, I also think that in play, the issue often isn't just loss of

skill; it's the beginning of repetitive behavior. And so it's very hard to sort out what's lost and what's something else is being acquired that supersedes the thing that's there.

Q So would a fair answer to that question, then, that you just aren't able to put a percentage on the number of cases of regression in which lost, acquired skills are lost in all three domains?

A That is something I could probably look at the data that we have and figure out, but I can't do it in my head.

Q And it's not anything that you've analyzed for publication, and there's not any data that we'd be able to look at right now to be able to make that percentage.

A Not right at this minute.

Q Okay. And finally, did you review the medical records of either of the individual child's?

A No.

Q Were you asked to do that by anybody?

A No.

MR. POWERS: No further questions.

MS. RICCIARDELLA: I have one followup for that.

//

FURTHER REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Mr. Powers again asked you about the current study, and whether or not you were able to come up with percentages based on data collected over the past few years.

Doctor, is your opinion in this case based on data that you've collected over the past four years, or your experiences over the past 35 years?

A Yes. I mean, the toddler study which I'm alluding to is just a small part of what I'm talking about. So mostly what I've been talking about has been the research that's been conducted prior to that study.

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER VOWELL: Any questions from my colleagues? Dr. Lord, I have no questions for you. Mr. Powers, did you have any followup to that last question?

MR. POWERS: No.

SPECIAL MASTER VOWELL: I wanted to get our questions in before we asked you.

MR. POWERS: Yes. Well, the last time that happened I was jumping up too early. But no, I have no further questions, thank you.

SPECIAL MASTER VOWELL: Then, Dr. Lord, you are excused.

(Witness excused.)

SPECIAL MASTER VOWELL: I take it we're going -- Dr. Fombonne is present. Do you need a brief --

MS. RICCIARDELLA: Can we have about a 15-minute break?

SPECIAL MASTER VOWELL: It's a good time to take our morning recess. My watch says it's 25 after 10:00, so how about we reconvene at 20 to 11:00.

(Whereupon, a short recess was taken.)

SPECIAL MASTER VOWELL: Please be seated. All right, we're back on the record in the case. And Dr. Fombonne is taking the stand. It looks as though, before we swear him, we have what appears to be Respondent's Trial Exhibit 12.

(The document referred to was marked for identification as Respondent's Exhibit 12.)

SPECIAL MASTER VOWELL: We're trying to get enough copies for everyone up here.

(Pause.)

SPECIAL MASTER VOWELL: Dr. Fombonne, if you would raise your right hand.

Whereupon,

ERIC FOMBONNE, MD

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

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

DIRECT EXAMINATION

BY MR. POWERS:

Q Good morning, Dr. Fombonne.

A Good morning.

Q Could you please state your name for the record?

A Eric Fombonne.

Q And would you please state your current academic position?

A I am the professor of psychiatry at McGill University in Montreal, Canada.

Q Now, you received a baccalaureate in science with distinction from the University of Paris, is that correct?

A That's correct.

Q And that was followed by medical school at the University of Paris, is that correct?

A Yes.

Q Do you have a medical degree?

A Yes, I have.

Q And you have a master's certificate in biostatistic methods and human physiology, is that correct?

A That's correct.

Q Now, I know that we qualified you, we went through your background in the Cedillo case, but this is a new record. So we do have to do this again in this case. And following medical school, where did you do your residency?

A In Paris.

Q In what field did you do your residency?

A In general psychiatry, and then child and adolescent psychiatry.

Q And when did you start specializing in child psychiatry?

A I did my training between 1977 and 1981, and then finished in 1982.

Q And do you hold any certifications in your field?

(Away from microphone.)

A Yes. The equivalent of it.

SPECIAL MASTER VOWELL: What did you say? The equivalent of what? I'm sorry.

THE WITNESS: The equivalent of the board

certification in France, which is the completion of a kind of a thesis, which gives you, grants you the title of specialist in child and adolescent psychiatry.

BY MS. RICCIARDELLA:

Q Is that the highest certification in your field?

A Yes.

Q And how long have you been working in the area of autism spectrum disorders, specifically?

A Since about 1986.

Q And what training have you had in epidemiology?

A I worked during my medical years, as a medical student I worked in various research projects as a part-time research assistant, where I learned many research skills in terms of conducting epidemiological studies, and also conducting randomized clinical trials.

I did my medical thesis, not my psychiatry thesis, my medical thesis on the particular statistical analysis of data in psychiatry from a clinical trial. I followed different courses in epidemiological methods. I went to a summer institute in New England in 1986, where I followed the three-

week course, intensive course, which was given by Ken Rothman, who is the author of the book Modern Epidemiology.

I followed various courses on genetic epidemiology analysis of longitudinal data sets, and other kinds of things.

Q Now, according to your CV, in 1989 you were recruited as a tenured research scientist at INSERM? What is INSERM?

A INSERM, it stands for the National Institute for Health and Medical Research. It's a state-funded research institute in France which, like the MRC in England, carries out most of the biomedical research in various fields of medical research in France.

Q And what were you researching while at INSERM?

A Mostly epidemiology in psychiatry. That's how I started my research career, by conducting the first epidemiological survey of child psychiatric disorders in France, in a population-based sample. It was the first time that it had been, it was done. That's how I developed my research career.

And then I did a lot of other projects in the field of epidemiology of autism, and then other things.

Q And how long did you hold the position at INSERM?

A I actually still hold it. I'm just on leave, permanent leave.

Q Your CV states that in 1993, you were offered a position at the Maudsley Hospital and Institute of Psychiatry in London, is that correct?

A That is correct.

Q And what is the Maudsley Hospital and Institute of Psychiatry?

A The Maudsley Hospital is one of the most ancient psychiatric hospitals in England. It has an excellent tradition for psychiatric care, both for adults and children. And the Institute of Psychiatry is the research institute or the academy component which is linked to the Maudsley Hospital, where a lot of research findings have been actually established over the last 30, 40 years. Both in the fields of social psychiatry, genetic psychiatry, and clinical trials. It's a very esteemed place in the world where many scholars have been spending time or sabbaticals. It's one of the, it's a mecca of psychiatric research, I would say, still now.

Q And did you work with Professor Sir Michael Rutter?

A Yes.

Q And what position did you hold there?

A I was initially appointed as a senior lecturer.

Q What is that?

A It's an academic position where basically you have a clinical appointment at the Maudsley, which is you're working in the National Health Service. And my clinical appointment at the time was actually to run the autism program that Dr. Rutter had been running for years, and take over his role in that clinic, alongside with some other colleagues.

I also established a clinic in the field of depression, in child and adolescent depression. So that was my clinical, my clinical part; that's the honorary appointment that academics have at the Maudsley.

And then my research piece was attached to the Medical Research Council Child Psychiatry Unit that Dr. Rutter was directing at the time. And I was head of the section on affective disorder research. And I was also quite heavily involved in the autism section of the same child psychiatric research unit.

Q Now, your CV also states that you are a Reader in epidemiological child psychiatry at the

University of London, is that correct?

A Yes.

Q And when approximately did you hold that position?

A I think it was about 1997.

Q Could you explain to the Court what a Reader position is?

A Yes. It's a British position. It's unique to the British system. So it's really where usually you are promoted from senior lecturer to professor, but there's a contingent of tenured positions. So they often create readership positions in recognition of the particular contributions of someone. And they usually, they create the position and give you the specific title, which recognized the particular area of expertise of the person.

So in my case, Kings College London, which is the university which organized all that, created this readership position. And they entitled it in epidemiological child psychiatry in recognition of my work in epidemiology and child psychiatry in general.

Q Now you're currently at McGill University, is that correct?

A Yes.

Q Could you describe your position at McGill?

A I have been at McGill since 2001. I am there the head of the Division of Child Psychiatry for the whole McGill University system, which involves three hospitals which are providing child psychiatric services.

I am also the head of the Department of Psychiatry at the Montreal Children's Hospital, which is the pediatric hospital of McGill University. And I am the Director of the Autism Clinic within the Montreal Children's Hospital. And I hold as well a, what is called a Canada Research Chair, which is a federal appointment, if you wish, which promotes research in my field.

Q And are you currently a full professor of medicine at McGill?

A Yes. I have a status of a tenured, full professorship at McGill.

Q And who do you teach currently?

A I teach to McGill University medical students in particularly in the domain of autism. I teach residents in psychiatry, whether or not they want to become child psychiatrists, but I teach a range of topics about nosographies, diagnostic assessments. I teach still in the field of depression treatments and and the field of depression, and of

course everything which has to do with autism.

I also teach quite a lot with, to pediatricians in our hospital. There are different research groups or clinical groups which want to learn more about autism. I teach to community organizations of pediatricians, of family doctors. Also, I teach in the community-at-large to groups of professors or, yes, mostly or community clinics.

Q And how long have you been teaching?

A Since I think 1983.

Q Are you affiliated with any hospital? You mentioned the Montreal Children's Hospital, is that correct?

A Yes.

Q Do you also give lectures outside of the formal teaching arena to professional groups or organizations?

A Yes, I do. I do give, I do grand rounds in several departments of psychiatry or medicine both in Canada and the U.S., and sometimes abroad. I do participate in conferences in my domain of expertise and particular associations to which I belong. I do also lecture in various conferences which are organized by family associations, which I have been doing for years.

Q Did you participate in a meeting last summer called Autism Europe?

A Yes.

Q What was that?

A That's one of the organizations which is a kind of federation of family associations. Both have a chapter in each of the European countries that they get together in this organization called Autism Europe. And they have a conference every three or four years. And they regularly invite scholars to talk about topics. I was invited last year to give a lecture on the topic of epidemiology and vaccines.

I was also helping them in terms of being a member of the organizing scientific committee for instance. So I do that quite regularly.

Q Now, you mentioned that you also lecture or devote time to family-based organizations, is that correct?

A To community-based organizations?

Q To community- or family-based organizations.

A Yes, yes.

Q Could you describe briefly what you do with those organizations?

A Well, what I have been trying recently often is to teach general practitioners, family doctors or

pediatricians about early signs of autism, and how to detect them early, and give them simple tools to, when they assess toddlers and they interview parents, to identify the red flags of autism, and try to point referrals to our program. That's one emphasis.

The other domain in which I've been teaching as well quite a lot is about the psychopharmacological management of children with autism in which I have a specific expertise and I run a particular psychopharmacology clinic in my hospital with a pediatrician for this particular group of patients.

Q Would you please name a few of the professional organizations that you are involved with, or a member?

A Yes. I am part of the Association of Chairs, of Academic Chairs of Child Psychiatry in Canada. I was the President of that organization for three years, a few years ago. And I am a member of the Canadian Academy of Child Psychiatry, of the American Academy of Child and Adolescent Psychiatry. I think others.

Q Were you involved in developing the diagnostic criteria for ICD-10 and DSM-IV?

A Yes.

Q Can you describe your involvement?

A I was involved in two ways. There was the development of the DSM-IV criteria for autism. It really followed a large empirical study, where data were collected in different centers worldwide. I think there were 16 centers, maybe even more. Where we had actually already developed ICD-10 criteria and DSM-IV criteria were being developed.

And we were comparing in the same children the ICD-10 criteria which we had proposed, the old DSM-III criteria or DSM-III-R criteria, and the proposed scheme for DSM-IV. So we were collecting data following assessment in our regular clinics using these different schemes.

And these were then sent centrally, and then analyzed to look at what kind of algorithm will be the best, and how we could make ICD-10 and DSM-IV closer in terms of the phrasing of the diagnostic criteria and the development of the best possible algorithm. So that was an empirically driven study, to really establish a database, a foundation to develop the criteria.

My other involvement in the DSM-IV was that with Dr. Rutter, I was involved for one year in negotiations, is a way to put it, on behalf of ICD-10 and WHO. We were working with, the working party of

the American Psychiatric Association, where there were about 10 or 12 American child psychiatrists who were preparing DSM-IV. And it had nothing to do with why autism was included, but all the other psychiatric disorders were examined. And we had several meetings about crosswalks, and how the two schemes were developing. And we tried to make them as comparable as possible, and that involved in particular a very long meeting in New York at one point between the U.S. group and the WHO group, which had actually three persons.

Q Do you currently have a clinical practice?

A I do.

Q As part of your clinical practice, do you diagnose and treat children with autism?

A Yes.

Q Approximately how many per year?

A It fluctuates, but I think my last year has been quite heavy. So I probably have seen 250 or 300 new cases last year. It was a bit exceptional. But that's what I usually -- so these are new cases. And I also have a caseload of children whom I follow, who for just regular followups, which sometimes extend to adolescence and early adult life.

And I also have this particular

psychopharmacology clinic, which is more for school-age children or adolescents or young adults who are already diagnosed, but have, present with severe behavioral problems which have usually failed to respond to proper behavioral interventions, and for which we consider the appropriateness of the use of medication to help reduce the maladaptive behaviors. That's a specific, highly specific type of work that I do.

Q Do you meet with parents as part of your clinical practice?

A All the time.

Q In what capacity?

A I meet them during the, in the assessments that I do. Currently I tend to see myself more complex cases now, or the cases involving our research programs, so I do the full assessment which involves from A to Z, that last, you know, it's usually several appointments with my team. And I do usually spend three to five hours for any child, including a long feedback session with the parents, which is sometimes followed by a followup meeting with them to deal with all the issues which arise.

So I do see a lot of families, young families who have children with autism. And I do meet

them, with them, in that kind of context, of course.

Q And you've been directly involved in epidemiologic studies of autism, is that correct?

A Yes. Yes.

Q Approximately how many, can you recall?

A I don't know.

Q Does 10 sound about right?

A Probably, yes. There were two in France, I think two or three in the UK, one or two in Canada. And I'm involved in one which is conducted with other colleagues in South Korea, and in the planning stage of one in Mexico and probably one in Russia.

Q And according to your CV, you've published over 160 articles related to childhood developmental disorders and behavioral disorders in general, is that correct?

A Yes.

Q Are those all peer-reviewed?

A Yes.

Q And you've published 34 book chapters pertaining to childhood psychiatric and developmental disorders, including the epidemiology of autism, is that correct?

A Yes. Many of these chapters relate to that topic.

Q And do you currently serve on the editorial board of any journals?

A Yes. I'm on the editorial board of I think four journals: The Journal of Child and Adolescent Psychopharmacology, European Journal of Child and Adolescent Psychiatry, the newly formed journal, which is called Autism Research, which is the new journal setup by INSAR, and The Journal of Child Psychology and Psychiatry.

Q Your CV states from 1994 to 2003, you were the Associate Editor of the Journal of Autism and Developmental Disorders, also called JADD. What is JADD?

A Well, it has been the leading journal in the field since 1971, when it was called the Journal of Autism and Childhood Schizophrenia at the time, when there was still diagnostic confusion. But it is, it was really the leading journal for both researchers at the time, but also practitioners. It has really a very wide readership, and has still a very wide readership, and covers a range of different topics, from treatment interventions and more fundamental basic sciences.

And now there are new journals which are emerging, which have more scientific or biologic focus

than JADD, which really didn't have much.

Q Are you currently a reviewer for any journal?

A Oh, yes. I review for JADD still, and of course the journals for which I am on the advisory board, and many, many, many other journals.

Q Now, your CV states that you were appointed by the National Institutes of Health as a permanent reviewer, is that correct?

A Yes. That was between 2002 and 2006. I was a member, a permanent member of one of the -- they changed the name, so it's one of the scientific review committee, one of the committees which are formed by NIMH to review grant applications, and classify them, and ultimately facilitate the funding of research. So I was on one of this committee.

I've been also appointed by the NIH as, in a special advisory board that they set up when they did, when they funded the CPA network and the START centers. A lot of the funding came in between 1996 up to currently, a lot of money has been going to fund and develop new research across different domains of research.

And NIH has set up a little advisory committee which has met with all the team leaders

usually once a year, to look at the progress of the science over these centers.

Q Did you have any responsibility for part of the textbook published by the American Psychiatric Association?

A There is one coming up textbook on autism that the American Psychiatric Association is preparing, in which I've been asked to write the chapter on epidemiology of autism.

Q Are you a member of INSAR?

A Yes, I am.

Q Is that formerly known as IMFAR?

A Yes. INSAR is International Society for Autism Research. And the meeting which is organized by INSAR is called INFAR. And I have been at INFAR involved initially in the publication committee, which led to the development of this new autism journal. And I was also part of the membership committee initially.

Q Did you just attend the last meeting of INFAR in London a couple weeks ago?

A Yes, I did.

Q You testified during the Cedillo trial, isn't that correct, Dr. Fombonne?

A Yes.

Q Other than that case, have you ever testified in court before?

A Once, in the case of, should I say the name?

Q Was it a Daubert hearing?

A Yes. Can I say that?

Q The Easter case?

A Yes, yes. It was a case in Texas about the same issue.

Q Doctor, I'd like to turn our attention to epidemiology in autism. First I'd like to just lay some foundations about what the different types of epidemiologic study designs. What are the different types of study designs?

A Well, epidemiology first is really the scientific discipline which examines the distribution of disease in human populations, and tries to identify factors which modify the distribution that we call risk factors. And different designs of different strength.

One of the strongest designs, what we call the ohort study, whereby you, basically you try to, you use observational data. I think a key aspect of the epidemiology that I do, that most people do, if we exclude from epidemiology the part of epidemiology which is experimental epidemiology, like randomized

clinical trial, where we can manipulate who is exposed to what. Most of the other designs rely on data which are occurring naturally, or are just observed by researchers in a way which we try to make meaningful to test hypotheses about mechanisms of underlying disease in humans.

And one way to do it is to have a hypothesis about a particular risk factor, an exposure to some kind of event, if it's a psychosocial event or a biological substance, and to look if this exposure in particular individuals lead to an increased risk of the incidence of the disorder when you follow these individuals over time.

So the design of these studies is really to have a group of subjects which is exposed, for whatever reason, to this particular risk factor of interest, and have a control group which is unexposed, not exposed to this particular risk factor. And then you follow them up over time, and look at how many new cases of disease occur in each of these two groups.

And then you compare the incidence in these two groups, in the exposed compared to the unexposed. And then you obtain some kind of measure of disease occurrence, which is called a risk ratio usually, and which is, if it is one, it means the incidence is not

affected by the exposure. And if the exposure has led to an increase in the risk of the outcome, you would have a risk ratio which departs from one, and gets higher two being sort of often the kind of risk ratio that we like to have, at least. So that's one of the designs.

Q The next kind, case control study. What is that?

A Yes. The cohort study is not really very practical if you have a very rare condition, because you need to study many, many, many subjects to have enough statistical power.

So when you deal with rare conditions, or somewhat less frequent conditions, and also because it's sometimes more convenient to do, we can ask the question in sort of a retrospective way.

So here we start from finding a group of people who have the disease that is of interest, and we find controls which are not suffering from the disease. And we ask retrospectively if they have been exposed to particular risk factors and we can move on to assess in if the cases have been more often than the controls exposed to this risk factor in their past. So that's a way to analyze the same question, but the design is retrospective.

And the key thing in case control studies is really sampling, in terms of you want to have a representative series of cases, and particularly you want to have a control series, which is representative from the underlying population which has given rise to the cases. So it's the art of the case control study often is in the choice of the controls.

Q So would it be fair to say that a cohort study is based on exposure outcome, whereas a case control study is based on -- I'm sorry. A cohort study is based on exposure, whereas a case control is based on outcome. Is that a fair definition?

A Yes. You design your study based on unexposed or exposed in the cohort study, and then you follow it for the outcome. And in the case control study, your starting point is the disease status, and then you look backward at what happened in the past in terms of risk exposure.

Q The next type of study is an ecological study? Or we'll go to prevalence study. What is a prevalence study?

A Prevalence study is a bit like a case control study, which is enormous and at the level of the population. But in essence, it's a photograph of a population at a given point in time.

And the question which is asked usually initially is to ask how many people in this population have the disease which I am interested in studying. So it's a very simple question. There is no passage of time, and you go in the particular population with techniques to sample people, assess their disease status. And then you end up with a prevalen proportion or prevalence rate, which gives you the extent of the magnitude of the problem associated with the disease in that population.

And then you can look at, under certain circumstances you can start to look also at risk factors which are associated with a disease, by using that design.

Q The final design, the ecological study. What is an ecological study?

A Ecological studies are usually considered to be of a lower level, in terms of the ability that researchers have to draw causal inferences between disease and risk factors.

The issue here in an ecological study is that usually you don't have, you contrast rates, rates of the disease and rates of the exposure. So you use aggregate data. So you look at trends in aggregates, rather than studying individuals in terms of their

exposure and their disease status.

So for instance, you could look at trends over time in a particular condition. It could be autism, it could be cardiovascular disease. And you could look at trends in diet, for instance, and look at the two trends that seem to correlate together. So you can sometimes find correlations which might be meaningful, but there is a lot of problems with these ecological studies. In some instances but not always.

Q Is an ecological study the same thing as a time-trend analysis? I see some studies describe themselves as a time-trend analysis. Is that the same thing?

A Yes. Time-trend or cross-national comparisons would be the same.

Q And I know you've prepared a couple slides to articulate some examples of ecological studies. We're now on slide 3.

A Yes. On slide 3, that's, for instance, studies on suicide have been using that particular design. So here you see, for instance, if you are interested in suicide you can see suicide rates going up over a period of time.

And then what usually people will do, they have an hypothesis about what a psychosocial situation

might be, which might be explanatory of the trend in suicide rates. Here in this particular case, you see that if you look at the rates of unemployment, it is going up, like the suicide rate is going up. And if you calculate a correlation, you can have a positive correlation.

And then the issue is how to interpret this correlation. So there is a well-known phenomenon which is called the ecological fallacy, whereby you can interpret this correlation as being, as meaning that it's the rise in unemployment which is leading to a rise in suicide.

In fact, you cannot reach that conclusion, because you don't know if those people who actually commit suicide in these populations over time are those who are unemployed. So maybe they are actually applying completely differently at the individual level than at the population level.

So that's what has been the problem and the difficulty with ecological studies, when you have trends which go in the same direction. Because when suicide rates increase over time, you can take anything which increased over time, and you will have positive correlation.

So if you look at another indicator, for

instance, now when you look at an increase in GDP, it's increasing as well. So that you would have a positive correlation, which might mislead you to interpret that as being causal, because you have a positive correlation.

Or you can have something else even. If you look at that, you have a decrease of gold value during the same period, then you have a negative correlation, which seems to indicate that the lower the gold value, the more people are at risk of suicide.

So these are a lot of issues which have been well described in the literature of ecological studies. That's when you have this kind of situation when you have something which is increasing, it will correlate with everything which decreased in the same period, or everything which increased in the same period. So there is a problem with interpretation in that case.

This problem is alleviated in a situation when you have natural experiments. So if you look at the other slides. So if you are to go back to the example of suicide and unemployment, for instance, here we have a different situation, because unemployment is not rising in a sort of linear fashion over the same period of time.

So if there was a relationship between unemployment and suicide, then we should see the suicide rates going up, and then plateauing, and then going down. So that is a situation where we can test more carefully if there is a causal connection between the two.

Q And just for the record, Dr. Fombonne is referring to slide no. 4.

A Yes. Then even better would be the next slide, which will be kind of a natural, an experiment of nature. Where here you have a risk factor, which is unemployment, which fluctuates. And you can look at if these fluctuations lead to corresponding fluctuations in suicide rates.

And then you have, for some reason, a complete discontinuation of the exposure. So the unemployment disappears. And you can see the suicide rates are keeping increasing. You can then thoroughly clearly say that there is no relationship between unemployment and suicide, because otherwise you would predict that suicide rates would at least fall to some extent when the, you have the disappearance of the exposure in this population.

So when you have a situation of that kind, which is quite rare, a natural experiment that we want

to capitalize upon, we can actually draw inferences in a much more solid way. I'm explaining that because it's relevant to the existing literature on TCVs and autism.

Q Doctor, what is meant by the term "prevalence rate?" We see that a lot in the studies.

A Prevalence rates are just proportions of, these are in studies where, at a given point in time you conduct a survey on a circumscribed population, and try to estimate in that population. So you have a denominator. You try to estimate how many individuals in this population have the disease of interest.

So it's the number of individuals affected by the disease in a population which forms the denominator population which is at risk for the disease.

Q Is that different from the incidence rate?

A Yes. The prevalence rate is a proportion. It goes from one to zero. Incidence is, in prevalence there is no passage of time. So it's just a photograph instantaneously.

Incidence means that you have observation which evolves over time. So you can, you start with people who are at risk, and then you follow them over time, and you calculate the new onset of disease in

that population at a given, at five-year followup or 10-year followup you calculate the proportion of people who have relapsed, for instance, or have died. These are incidence data.

There are different forms of incidence rates, but I don't want to get into that now. The idea of incidence that you have, you observe people over time.

Q Turning to the area of autism diagnoses in the United States, has the number of diagnoses increased in the United States over the years?

A They have.

Q And we're looking at slide 6?

A I'm now on slide 6, which is the, represents the results published in early 2007, one of the two major surveys conducted by the CDC. These particular slides give the results on eight-year-olds which were surveyed in 2002, and therefore they were born in 1994. That represents incidentally the population size of children who have been surveyed is about 410,000 children eight years old in the U.S.

It's a large study which is conducted in 14 states. And the prevalence here is indicated in the little orange squares. And the average population here, and here we're not talking about not autism

narrowly defined, but we are talking about autism spectrum disorders. And there was no differentiation in that study between narrowly defined autistic disorder and PDDNOS. They are all grouped in the same case definition.

And the average rate in that particular study is 6.6 per 1,000. Or another way to express that is 66 per 10,000. And just to give some equivalences, because sometimes people don't know, but 66 per 10,000 is 0.6 percent. It's also one child is 150. These are all equivalent ways to express the same findings.

Q Slide no. 7. Slide no. 7 is 66 out of 10,000. Is that the current prevalence rate of ASDs in the United States?

A Yes, that's the best estimate that we have today. And this estimate is highly consistent with studies which have been performed in the UK in recent years, in many, many areas in the world, including Denmark, including the Faroe Islands, including Canada. They have all come up with research more or less in the 60- to 70-per-10,000 range, with some exceptions. Some studies are showing higher rates, some studies are showing slightly lower rates.

But if we can go back to slide 6, I think

what one issue, one interesting observation on this slide is that the average of 66 per 10,000 is an average. So it's an average for the years in these 14 states.

But if you look at the state's specific prevalence estimate, it's actually quite variable. You have an extreme on the right-hand side of New Jersey, where their rate is actually 1.06 percent. That is the highest rate in the U.S. in this particular CDC survey. So that's high.

And then you have, on the third column from the left, the state of Alabama, the rate is 33 per 10,000. So it means that in the same study, you have in a state a rate which is as low as 33, and in another state you have a threefold increase in the rate.

So even at the same point in time in the same country, you can have threefold variations in the rate, probably and that's how the CDC explained it, is because the ascertainment of cases in Alabama was four, and much better in New Jersey. So it's important to recognize that, because differences in prevalence rates do not mean that there is an epidemic of autism in New Jersey, or that living in Alabama protects you against autism.

Q Now, Doctor, I'd like to talk about the studies that have been done that looked at a possible causal association between thimerosal-containing vaccines and autism. And on slide 8 we just put together the nine studies that you discussed in your report, is that correct?

A Yes.

Q I'd like to first turn to the Hviid study, the 2003 study that appeared in JAMA. We filed this, well, it's been filed as Petitioner's Master List 238. Doctor, when was this study published?

A It's published in the prestigious journal which is called the Journal of the American Medical Association.

Q Is that a peer-reviewed journal?

A Yes.

SPECIAL MASTER VOWELL: One moment, please. We're moving from slide 8 to slide 9 now.

MS. RICCIARDELLA: Yes. Thank you, ma'am. We are now on slide 9.

BY MS. RICCIARDELLA:

Q Is that considered a well-respected journal?

A Yes. It's one of the journals, medical journals which has a very high-impact factor.

Q And what type of study was this?

A So this is a cohort study. It's based on the National Register which exist in Denmark, where they collected everybody that has a unique identifier and they have large database where they have, they follow people in terms of their medical diagnoses of different kinds, coded in ICD-9 and 10 and before, it was 8. And there are also different registers, like they have a register on immunization, for instance, so they could really merge these two registers and look at -- and they could recreate retrospectively a cohort study by looking at children who were born between 1990 and 1996.

And then because in Denmark there was a discontinuation of thimerosal in 1992, you have, in that sample you have children who had been exposed to thimerosal-containing vaccines. And they knew exactly which vaccines, what was the amount, and other children who had been unexposed to these vaccines. So you can then follow these two groups, exposed and unexposed, and see if the incidence of autism when you follow them up to the year 2000, or to diagnosis occurring. See if the incidence in those who have been exposed to thimerosal is higher or equal to those who have been only vaccinated with thimerosal-free vaccines.

So that's the design of the study. It's quite powerful, because that's the kind of strong study we want to have. And just to give precision, that study has in its sample size almost half a million; 417,000 children if I recall well. So it's really, in terms of sample size, extremely precise.

Q And what were the results of the study?

A The results of the study was that they looked at the association in different ways. They first compared children who had received all thimerosal-free vaccines, compared to children who received at least one thimerosal-containing vaccine. And they found that the incidence in both groups was not different.

And the other way that they looked at it was they looked at dose response. They looked at how much thimerosal-containing vaccines, children who had been exposed to these vaccines received, to see if the risk of autism was increasing as a function of the dose received of thimerosal. And again, they looked at that, they couldn't find any evidence of a dose response of a threshold at which the risk would suddennly increase.

Q Dr. Greenland criticized this study in his report as being really not informative to the issue at

hand today, because the dose of thimerosal received by children in Denmark differed from the United States. Do you agree that this study is irrelevant to the question before the Court?

A You know, it is absolutely relevant, in terms of it examines a range of exposure, which is from zero micrograms to a maximum of 125 micrograms. So in that sense, it doesn't go beyond that limit, that level of exposure, and doesn't really test for risk associated with higher level of exposure.

However, in Denmark, if you look at the schedule of vaccinations, Danish children at the time of thimerosal-containing vaccines, when they were at three months old, were exposed at that age to what American children were exposed to. In that sense, the exposure up to age three months is comparable in that study to what happened in the U.S. It's not, it cannot be dismissed in terms of being informative.

And again, at the very least it tests for a range of exposure, which is from up to 125 micrograms.

Q I noticed that in slide 9 you have a section called "limitations," and you note what the maximum exposure was.

A Yes.

Q Does this affect the validity of the study?

A Not validity. It depends on what you call validity. It affects what we call external validity, so it does not, the findings cannot be generalized to populations where the exposure has been higher than that. That's what we could say.

There are many strengths in that study, including the fact that because the children were unexposed to thimerosal-containing vaccines, they were not unexposed because of medical contraindications. They just were unexposed because of a change in the fabrication process of vaccines in Denmark. So they were, in terms of indications, the same type of groups as those who were exposed. That's a very important aspect of that study, because it means that the unexposed controls were very likely to be completely similar to the exposed children.

Q The next study I'd like to look at is the Verstraeten study. We are now on slide 10. And this has been filed as Petitioner's Master List 247. When was this study published?

A In 2003.

Q In what journal?

A In the Journal of Pediatrics, which is a highly reputable journal in --

Q Is it a peer-reviewed journal?

A Oh, yes.

Q And what type of study was the Verstraeten study?

A Again, it's a cohort study where they used the VSD to recreate retrospectively cohorts of children, and look at their exposure to thimerosal, and look at the incidence of autism as they follow them up. So it's a cohort study.

The fact that the design was interesting in the sense that they started with two HMOs, and they wanted to look at a range of outcomes -- autism was one of them, but they looked at also other neurodevelopmental outcomes. And these outcomes were selected a priori based on existing published findings from the Faroe Islands. They really looked at what was concerning people at the time.

So they selected their outcomes very well. And they decided to look at two HMOs first, and then they decided we're going to look at HMOs, and look only at those conditions which occur in a sufficient number of children. And they set up a criteria of there must be at least 50 children presenting an outcome so we can look at the association, which is reasonable to do.

And they said if we find something, some

kind of association in one of these two HMOs in a number of children, then we will look in the third HMO to replicate our findings. It was a nice design in the sense of they wanted to generate findings initially, and then replicate them in a separate sample, which is a very nice design when it works well.

Q What were the results of this study?

A They looked at it in different ways. The exposure to thimerosal, they looked both at the quantity of thimerosal received over the, from birth to age seven months. But they looked also at levels, different levels of thimerosal exposure. And both ways using exposure as a continuous variable, or as a categorical -- a variable. I hope I'm not too technical. Maybe a bit.

So anyway, they couldn't find any association with autism. So there was one HMO, which is HMO B, where there were 202 children with autism identified, where they could conduct the analysis. And the analyses were negative looking both ways.

So I think the strengths are that the HMO B had a large population, 110,000. It's VSD database has been used to examine to do prospective studies to look at vaccine adverse effects. And in that

particular study, one of the advantages that they could test up to levels of exposure which were meaningful for the U.S. concerns, because the exposure levels were up to the value of 87.5 micrograms. And they also did a diagnostic confirmation on children with autism in HMO A and B, and found that there was a reasonable, that the electronic codes were confirmed by medical record review.

Q Do you consider the Verstraeten study to be a valid study?

A I do. I of course am aware of the controversy which surrounded that, I think from an external perspective what they have is extremely reasonable and for me it's a perfectly acceptable study.

Q I'd like to turn now to the Stehr-Green study. And we're on slide 11. That has been filed as Petitioner's Master List 230. When was this study published?

A In 2003, in the American Journal of Preventive Medicine.

Q Is that a well-respected journal?

A Yes.

Q Is it a peer-reviewed journal?

A Yes, it is.

Q And what were the results -- first of all, what type of study is this?

A This is an ecological study. And you see here one of the findings, and the starting point of this analysis was to look back at what was presented at the Institute of Medicine Committee in 2001, when someone drew a correlation between increasing levels of thimerosal in California and increasing numbers of children diagnosed, pretty much the two lines I showed at the beginning, and showed there is a correlation. And therefore, thimerosal is the causal factor of the increased numbers of autism.

So they say well, let's look at that. That's what we see in California, but let's look at what happens in two Scandinavian countries where, in fact, we have a different situation again, an experiment of nature where in Denmark, in 1992, I think it was in March or April, they discontinued the use of thimerosal in the production of vaccines. So there was a way to test if this discontinuation was followed by a fall in the rates of autism.

In Sweden it was the same scenario. They discontinued thimerosal in 1993 altogether. And you could see here on this particular graph, it applies to the inpatient population of Sweden. I think these are

children which are age two to 10. And you can see that the bars indicate the level of thimerosal, and then it decreases progressively, and in 1993 onwards there is no longer any thimerosal in the vaccines.

The same graph can be found from Denmark in the same paper. And what is remarkable in these particular three comparisons, Denmark, Sweden, and California, is that first, the rates of ASDs started to increase before there was any change in the levels of thimerosal, both in Denmark and in Sweden. So irrespective of if there was no change in thimerosal level, and the rates started to increase. And they started to increase at about the same time in Denmark, Sweden, and California.

But then what happened is the rates of increase continued throughout the period of observation, even though, in Denmark and in Sweden at different times there was a total discontinuation of thimerosal. So that really showed you that when you have variation in the exposure level, you have a much more powerful test to look at these correlations than you do in ecological studies. And when you have this opportunity, the findings of California did not hold true.

Q I'd like to turn now to the Madsen study,

which is Petitioner's Master List 239. We're on slide 12. When was this study published?

A In 2003.

Q In what journal?

A In Pediatrics again, the very well-known journal.

Q And what type of study is it?

A This is again an ecological study. And that study looked at the rates of -- it's again relying on data collected in national registers. They are coded in various schemes, ICD-8 first, and then ICD-10 I think in 1993 or 1994.

And they look at rates of autism in different age groups, two to four, five to six, seven to nine. I think there are two interesting findings, one which is not fully appreciated maybe in the paper, which is that before 1970 in Denmark, the schedule of vaccinations implied that children who were exposed to levels of thimerosal which were of ethyl mercury, should I say, of 200 micrograms. So the level of exposure in children in Denmark in the sixties, up to 1970, was very high, actually comparable to what happened in the U.S. in the late nineties.

And you can see here at the beginning of the period of observation, 1970 up until 1976, it's

lagged. So basically you can see that those children, some children in these age groups were exposed to high levels of ethyl mercury, and there was absolutely no evidence at the time of an epidemic or high rates. So this is one story.

And then in 1992, this is where the vertical line, actually the line here should have moved. But in 1992, in March or April, there should have been -- they discontinued the use of thimerosal in vaccines. And if you look before 1992, you can see the beginning of the increase in the rates of ASDs in two of the three age groups. And so it starts before there is any change.

And then, when thimerosal is discontinued, you can see that the rates of increase are the same. There is no downward trend that you would predict if there was a strong association between thimerosal exposure and the risk of autism. Again, it's looking at a natural experiment with the total disappearance of an exposure; and therefore, if there was an association, you should see some kind of effect.

Q What conclusions did the authors of the Madsen study draw with respect to thimerosal-containing vaccines in relationship to autism?

A Well, they concluded that there was not much

evidence of an association between the two.

Q Doctor, are you familiar with the 2004 IOM report that's been filed as Respondent's Master List 255?

A Yes.

Q And does that report contain a discussion of the Hviid, the Verstraeten, the Madsen, and the Stehr-Green studies that you discussed today?

A Yes.

Q And what conclusions did the 2004 IOM committee draw with respect to those studies?

A Well, at that time they received findings from these epidemiological studies. And they said that these epidemiological studies were informative for the debate about causation, a situation which was new compared to 2001, when there were actually no epidemiological studies available in humans about the effects of thimerosal-containing vaccines. And that, alongside other kinds of data, led the committee to reject the hypothesis.

Q I'd like to look at some studies that came out after the 2004 IOM rendered its report. I'd first like to look at the Andrews study that's been filed as Petitioner's Master List 4. We're now in slide 13. When did this study come out?

A In 2004, in I think September, in Pediatrics.

Q In the Journal of Pediatrics?

A Yes.

Q Okay. And what type of study was this?

A Again, it was a cohort study. It's again a study where you can follow up over time children where you know how much immunizations they had received, and look at how many developed autism, and if there is a relationship between the amount of thimerosal exposure and the risk of autism.

So it's a cohort study. It's population-based, because the study sample is from a large electronic database, which is called a GPRD, which contains probably currently about four million people. So it's really a large electronic database, which has been shown to be varied in many ways.

And the results for autism are shown here. They looked at in terms of how many children received their dose by three months of age, or by four months of age. And they looked at the relationship between number of doses received and the risk of autism, and found that there was no relationship.

And again, the Hazards ratio were below one, and the confidence intervals were actually quite

narrow, because the sample size is large. And when the last column on the right is looking again at the same exposure, but in a more continuous fashion, and taking into account the age at which the child received the vaccination. So that if a child received the full vaccination complement at an early age, in fact his dose of thimerosal considering his age and weight is somewhat higher. And this factored in the analyses, and it shows again no effect.

There also in that study, I should say which is an advantage, looked separately at a sample that I think had about 2,500 preterm infants.

Q Preterm?

A Preterm infants. And they couldn't find in this group, as well, any association between -- and the importance of the preterm group is that because they are usually of low birth weight, the relative dose they receive relative to their weight is higher. So their exposure is, in effect, relatively higher than normal-term babies.

Q The next study I want to look at is Jick and Kaye, which has been filed as Petitioner's Master List 92. And we're on slide 14. When did this, when was this study published?

A In 2004. I think it was later in the New

England Journal of Medicine, but yes, I think that's what it was.

Q What type of study was this?

A So that's another design. It's a case control study. And they again used the same UK GPRD database. And that case they looked at in this database, in particular years, children who had a diagnosis of autism, and they matched controls. And the five controls for one case to increase their statistical power. And they were well-matched. And they looked at, you can see here under the main results is that if you look at cases of autism, 96 percent of these children had been exposed to thimerosal-containing vaccines under exactly three doses of DPT vaccinations. And it was the same proportion of controls who had been exposed to the three DPT vaccinations.

There is no difference in terms of exposure to the DPT vaccinations between children with autism or matched controls.

This study is interesting, because it's a case control study nested in a population-based cohort, so there is a good representativeness of the sample, although the sample is small. Which is a limitation of that study.

Q The next study I'd like you to look at is the Heron study. We're on slide 15. The Heron study has been filed as Petitioner's Master List 14. When was this study published?

A 2004.

Q In which journal?

A In Pediatrics. And this is now slide 15.

Q And what type of study is this?

A This is called the ALSPAC study. It's done in Avon, in the southwest of England. And it's a population-based prospective cohort where women have been, 13,000 I think women have been recruited during pregnancy, and their children followed up at multiple waves of data collection. And this is an ongoing prospective study.

So the importance of that is that it allowed, the data collection allowed researchers here to look at the effect of multiple confounding variables, which were often not available in the analysis of other cohort studies or a more limited set of variables could be assessed for their confounding role.

In that study there is a range of outcomes which have been looked at. And most of the outcomes are actually negative, with the exception of one out

of 69.

Autism was not assessed directly in this, in this paper, but because I have worked in the UK, and I know that children with autism are usually, have a statement of their needs with the local educational authorities. So the line which is here, which says LEA, is a group of children which would typically contain a high proportion of autistic children. We don't know how high it is, but that's where they are.

And in a way, although it's a proxy measure for autism, one can see here that irrespective of the way you look at the association, there is no association between this category of special needs and exposure.

Q The next study I'd like you to look at is one I'm sure you're very familiar with, because you did it.

A Yes.

Q I'm referring to slide 16. It's the Fombonne, et al. 2006 study, filed as Petitioner's Master List 40. What journal was this published in?

A In Pediatrics.

Q And what type of a study was this?

A So this is again an ecological study, where we identified in a school board in west Montreal, all

children with a PDD diagnosis. And we were interested in prevalence, initially. And found a prevalence of 65 per 10,000 in that particular population.

And then we looked at, we again capitalized on the experimental nature in which in Quebec during that period of time, there were changes in the immunization schedule. And the content of thimerosal of the vaccines which were used in Quebec.

So at the beginning of the period, from 1987 to 1991, there were medium levels of exposure to thimerosal, around 100 or 125 micrograms. And then because of the addition of new vaccines, there were three or four birth cohorts exposed to levels of 200 micrograms, comparable to what happened to the U.S. in the late nineties.

And then, because they changed the vaccination system of production, then the last birth cohorts were actually exposed to thimerosal-free vaccines. So we had a nice way, in this ecological study, to test whether the trend in the risk of autism in that particular population was affected in any way by variations in the levels of exposure, and by discontinuation of thimerosal altogether. And we found absolutely no relationship between the two.

And moreover, in those children in the last

birth cohort, and therefore vaccinated with thimerosal-free vaccines, the average prevalence in that particular group of cohorts was about 80.6 percent -- per ten thousand, significantly higher than the prevalence for all previous thimerosal-exposed cohorts.

Q The next study I'd like to look at is Schechter and Grether. We're on slide 17. That's been filed as Respondent's Master List 439. Are you familiar with this study, Doctor?

A Yes, I am.

Q What type of study is it?

A It is an ecological study.

Q And when was it published?

A In the prestigious journal called Archives of General Psychiatry. It's one of the, in the field of psychiatry one of the most reputable.

Q And when was this study published?

A In 2008, early -- 2008.

Q And what were the results of this study?

A So they, the idea again was to look at what would happen in California. California has a unique data set, which is a developmental, the DDS database, I don't know what --

Q The Department of Developmental Service?

A Yes. They have a database which has it's own limitations, which at least allows to evaluate some trends. And as everybody knows, following the recommendation of 1999, there was a progressive discontinuation of the use of thimerosal in the vaccines which were used in the U.S. Although the exact timing of the total discontinuation in vaccines is difficult to ascertain, and there are no good data for California in terms of exposure to thimerosal for the cohorts in 2000, 2001, 2002, and 2003.

People were expecting that if there was an effect of thimerosal in the risk of autism, we should see a drop in the number of children referred to this public service; and that this drop should be seen starting in 2004 or 2005, where children that were thought to be diagnosed would have been mostly unexposed to thimerosal-containing vaccine.

And that's what they have done here. If one looks at the lower line, the lower line is the number of children with autism, or ASDS, for each quarter. They use each quarter, the data are produced for each quarter, so it's a number of new cases.

Here it looks only at children who are aged three to five. So by the end of 2003, we would have expected a decline if there was an association. And

thimerosal becomes phased out. And you can see that between 2004 up to 2007, there is absolutely no evidence of a drop in the numbers. And in fact, the rates and the slope of the increase in the numbers of children referred to this service is the same as before.

I think what another message of that study is, is that the upper line is actually looking at children who have developmental disabilities that group includes autism, but other kinds of condition, as well. And you can see actually this group increases over time in the three- to five-year-old as well, which seems to come out of different studies which have looked at these trends over time in various years data sets.

Q So what are the conclusions of the Schechter and Grether study?

A That their study really does not support any connection between thimerosal-containing vaccines and the risk of ASD.

Q Now, you've included another study in your report that didn't look specifically at autism. I'm referring to the Thompson study that's been filed as Petitioner's Master List 192. And we're now on slide 18. Why did you include the Thompson study in your

report?

A Because it had relevance in terms of various neurodevelopmental outcomes which have been postulated to be increased following thimerosal-containing vaccines. So there are some data which are conflicting between the Seychelles and the Faroe Islands study in terms of method, okay. We didn't have, up to that study, a good study looking at the range of neurodevelopmental outcomes following thimerosal-containing vaccines.

So this study is unique and new in that respect. It's done by the CDC. It's looking at over 1,000 children. This is a cohort study of children who were all born between 1993 up to 1997, so that guarantees that there is a range of exposure in this particular cohort.

And they looked at, they followed them up, I think up to age seven, or maybe 10. And they invited the children and their families to have direct assessments. So these children are assessed directly by psychologists who are all blind to the amounts of vaccines or thimerosal received by the children.

And they used actually 42 developmental outcomes. And they basically looked at all the possible associations, by gender and all cohort

genders combined, and concluded that there was no evidence for an association between thimerosal and neurodevelopmental outcomes.

Autism was not part of this study. It's just like other kinds of outcomes in terms of speech delay, language delay, IQ, other kinds of outcomes.

Q In what journal --

A But there were a few significant findings which were representing statistical random facts.

Q In what journal did this study appear?

A It's the New England Journal of Medicine. It's a strong study. They have a somewhat low rate of participation, which I calculated to be 54 percent. But there is no reason to believe that there would be a strong selection bias associated with this relatively low participation rate, particularly because they could show that nonparticipants in this study compared to participants had the same type of exposure distribution at baseline.

Q Doctor, we have been looking at these studies individually. But do you have an opinion as to what the studies say collectively as to the issue before the Court here?

A Well, I think what has been discussed before, each study has its own limitations in terms

of, you know, how much control of confounding you can have, and the range of exposure which is tested. But what is quite striking is that first, no study has shown that there will be a risk ratio which would depart from one, suggesting that there would be even a trend towards an increase in the risk of autism. All studies show a risk ratio of close to one. Often, actually, on the left-hand side. So there is no evidence whatsoever there is a trend that could be detected.

I think that secondly, that the findings for me, although each study could be criticized, is that there is consistency across different populations with different study designs of the findings. And this is what I think makes the state of epidemiological findings in the study of this hypothesis quite robust, in allowing us to further reject this hypothesis.

Q Okay. Now, other than the epidemiologic studies that you discussed today and in your report, are there other studies that you think are relevant to the question of whether thimerosal-containing vaccines cause autism? Now we're on slide 19.

A Yes. I think the number of facts that should be brought in mind, the first thing is that when we look at the Faroe Islands, for instance, or

other studies which have looked at methyl mercury exposure, there has been no evidence ever reported that autism or PDD was an outcome of methyl mercury exposure or intoxication. So that's something to bear in mind.

The second thing is that when one looks at the prevalence of PDDs in different populations, there seems to be no relationship between the levels of PDDs or rates of PDDs, and how much thimerosal the vaccines contain. So just to give an example here, there is a study now published on the Faroe Island population which shows a rate of 56 per 10,000 in this population, whereas we know they are exposed to high levels of methyl mercury.

And I could give more examples of that. There are some studies, for instance, like recent data from Denmark where, if you look at children born after 1992, their rates are now in the range of 62 per 10,000; so again, consistent with other rates. And in the thimerosal-free population zero micrograms, the rate is 62. In the UK, there are multiple studies where the level of exposure is 75 micrograms, multiple studies showing rates of 60 or 70 or even higher than that.

And the rates in the U.S. based on the CDC

studies are not higher, despite the higher exposure to thimerosal. So there seems to be no consistency in the relationship, at least on the ecological level, between what's happening in terms of thimerosal exposure and the rates, appearance rates, of autism.

Q Okay. Doctor, are you aware of the existence of epidemiological studies that purport to show an association between thimerosal-containing vaccines and autistic disorder?

A Yes.

Q Are those the studies done by Mark Geier?

A Yes. I mean, the only exception to the consistency which I mentioned is the group of studies, published by Geier and Geier, and including the most recent one by Young, Geier, and Geier. And if one looks at their earlier studies, I mean, they have been reputable for having methodological flaws, which are so major that their contribution to the debate has been actually rejected by the IOM community, and saying that their studies were actually not contributing to the scientific information.

Q Were those studies conducted using accepted epidemiological methods?

A No.

Q Do you agree with the criticisms that the

IOM committee put in their 2004 report pertaining to the studies done by the Geiers?

A I do.

Q Is it accepted practice in the epidemiologic community to rely on study results that are considered uninterpretable?

A No.

Q Have you reviewed the recently published study by Young, Geier, and Geier that's been filed in this litigation as Petitioner's Master List 665?

A Yes, I have.

Q And do you consider this to be a valid study?

A No, it is a flawed study.

Q Now we're on slide 20. Could you explain why you don't consider this to be a valid study?

A Well, there are many flaws in the study. Again, I think it's using the VSD database, which is actually a nice database to do cohort studies, and they did not use that to do a cohort study or to do a case control study, which is a mistake. A shame. And instead of that, they constructed an ecological study based on this dataset, which is bad.

There are multiple issues in that study in terms of statistical analysis, but I just wanted to

draw the attention of, on this graph, which is what they showed is this black line is what they estimate to be the level of thimerosal exposure in different birth cohorts in that particular database.

The database has about over 200,000 subjects. And they construed their exposure data in a way which is very hard to follow, and they actually do not provide the detailed calculations. And again, as in many of their papers, you cannot actually verify what has been done.

But if one looks at this, they did a poisson regression, which is a complex statistical analysis. But it boils down to being doing a regression. So if you look at the bars of the rates, what they estimated as being the prevalence rates in each birth cohort in that database, from between 1990 to 1996 -- so these are the bars. And then the black line is the level of thimerosal exposure. And they report a strong correlation.

And if one looks at this correlation, if one looks at the three left-handed bars, you can see that there seems to be a strong correlation, because you have a steep increase in thimerosal exposure, and the prevalence is increasing during that three years.

Now, if you look carefully at the paper, in

each birth cohort they had about 40,000, 50,000 -- I should check the numbers -- but in '91, '92, and '93, they have 15 percent of their sample is between '91 to '96.

The bar in 1990 contains only 0.6 percent of their sample. So it's based on 2,000 children at most, as opposed to 40,000 in all of the other bars.

So we are now, they are doing like a correlation where in fact the first data point which serves the coalition extremely well is actually based on a very limited sample size.

When we do correlation in general in psychological sciences, when we have outliers, we try to see if an outlier is actually driving the correlation in one direction. We call that plots of influence. And if this data point influences the correlation, we remove it.

In that particular study, they didn't recheck that. And I suspect they didn't check, because if you check it and if you remove that data point, what you would see is the correlation actually disappears in the first four years. There is no, you have a flat line, okay? That's one point. I really find that it is data manipulation.

And if you look on the other part, on the

three, the two bars on 1995 and 1996, if you read carefully the paper, in fact, these bars are false. They just are based on so-called adjustments that they have made because they think that there is a truncated followup, which is probably correct, but they added numbers of children. So these bars are actually not observed numbers of children. They added 45 cases in 1995, and 80 invented cases in 1996.

So the actual observed numbers are more like what the white sections of the bar are showing. And they added the red sections to make up for some kind of unobserved subjects.

It can be sometimes useful to do some form of imputation techniques to address missing data, or censoring, as we call it. But this is just data manipulation, again. And in fact, they just added numbers which do not exist. And if you read carefully their paper, that's what they are doing. And if you remove these adjustments, you have no correlation at the end between the thimerosal increase and the actual observed.

So between data manipulation and the -- I think this study is not acceptable at all.

Q Doctor, I'd like to turn briefly to the issue of regressive autism. Is it restricted to

autistic disorder only? Regression?

A No. No, I think that it varies. It varies across studies. But in most studies which I have seen, including the Dr. Lord studies and recent studies by Hansen, et al., for instance, shows that the rate of regression, however you define it, seems to apply across PDDNOS as well as autism.

Q And is it a new phenomenon?

A No, it is absolutely not new. This is just an excerpt of the British literature in 1964. And you can just show the case one by --

Q We're on slide 21.

A On slide 21. And you can see descriptions. This slide was chosen in particular because at that time there was no measles vaccines at all in use. But anyway, it's an historical slide which shows that regression has been described clinically for decades, and including at the beginning by Leo Kanner.

So it's not a new phenomenon, and it was important to recognize it because of the fact that I recall during my training, psychiatrists were interviewing mothers who were reporting this phenomenon, were actually dismissing that, and were saying that the mother was fabricating this experience. So some people were trained with a

psychoanalytical mind.

So it's an important phenomenon to recognize, because it's actually part of the experience of parents, and has been a part for decades.

Q What is the current rate of regression?

A It depends how you define it. I think I completely agree with Dr. Lord. It will depend how much, how stringent are the criteria that you use to define regression.

If you want to be sure that in order for the skill to be lost, you want the skill to have been shown consistently, as we sometimes do in questions which are embedded in the ADI; if you have such a strict definition, we'd have a lower rate. If you broaden your definition, you'd have a higher rate.

So the rates are anywhere between 15, 13 percent, 35, even more in more recent studies. I think we have paid attention more to this phenomenon. In the ADI, for instance, there has been improvement in the questions which are looking at regression as a result. The new studies are documenting in a better way more subtle types of regression, and therefore the rates are likely to be more around 30 percent, 40 percent.

Q Now, on slide 22, you've prepared a brief chart on a study published by Hansen called the CHARGE study. Why did you include this study in your presentation today?

A Because it's very recent, and also because it's based on a population-based sample from California. So it's just very informative again for our debate.

Q What does the study tell us?

A And it has a large sample, so it's a large sample of 333 children. And they used standardized measures, like the ADI.

And the study shows very interestingly that again, depending on how you define regression, you have different rates. So if you look at children who lose both language and social skills, the regression rates are 15 percent in that study. But if you look at, if you add to this 15 percent those who just lose either language skills or social skills, it's another 26 percent. So the combined rate of losing either skills or both skills in that study in particular is 41 percent.

But I think the other interests of including this study -- and there are many more -- is that they again looked at whether or not this regressive form of

autism has distinctive characteristics as a phenotype which might merit that it would be treated differently.

The way we validate syndromes again or phenotype syndromes in psychiatry in particular is that we define clusters of behaviors. But in order for these clusters of behaviors to be meaningfully different, we need to look at evidence of correlates which are different. So they should be correlated to different family history, correlated to different biological marker. They should have a different treatment response.

So we look at these indices to see whether or not these are two different phenotypes, or whether or not they are just variations of the same phenotypes. And that study, alongside many other studies, has again failed to document that the phenotype of regressive autism is different than the normal regressive phenotype.

So they looked at gi symptoms, seizure history, sleep problems. And most of the clinical characteristics, adaptive behaviors, language levels, there were just a few borderline significant findings in terms of, as found, by the way, by Dr. Lord, that their communication skills were slightly lower than

the normal regressive type. But otherwise, they looked pretty much the same.

And the difference in terms of expressive language levels of communicative behaviors were significant, but not clinically very meaningful. Like two or three points on the vineland, something which is not regarded as -- and that's the way they compute it.

Q Let's turn to slide 23. It discusses a study that you did in 2001, and published in the journal Pediatrics. It has to do with regression. What was the goal of your study?

A The goal of the study was to look at the MMR-induced putative phenotype. But the point of showing this slide today and the next three slides is to look at studies where we can assess trends over time in the proportion of regressive autism. So I'm not interested at all here in the actual level of regressive autism, because it will vary from study to study based on the definition and the tools which are used.

But within each study, the definition has been maintained constantly. That's what helps us to assess whether or not it has increased or not.

Q And what did your study conclude?

A In that study, you could see in that study there was no difference over a period of about 20 years in the proportion of regressive autism, in children who were assessed at the Maudsley Hospital using a common instrument, which was the ADI.

Q And slide 24 refers to a study done by Honda. That also looked at whether or not rates of regression have increased over time.

And what were the results of that study?

A Again, you can see the proportion in the gray shaded area, which are in the lower range, are the proportion of regressive autism. And they fluctuate in line with the overall numbers of the cases of autism. And therefore, there is no evidence that over that period of time, which is eight years, there is a change in the proportion of regressive autism in that particular study.

Q Slide 25 refers to a study done by Taylor in 2002. What did that study find with regard to rates of regression?

A There was a study based on, I recall, 450 children with autism assessed in the northern part of London in the UK. And the average rate of regression was 25 percent, based on, I think, on a record review. But the trend over time is non significant again. So

there are fluctuations from year to year, but there was no evidence for an increase.

Q Slide 26 refers to another study that you did.

A Yes.

Q Looking at rates of regression. And what did you find in your study?

A That was the validation study that we published based on our GPRD case control study of autism and MMR. So we have looked at records on I think it's what, 300 or more children, no, 178. And we rated regression in that study. And the only line which is important is that which starts with regression. And by different periods, you can see that in that record review, the rates of regression fluctuate between 7.6 percent to 31.7 percent, and the trend is absolutely non significant.

Q And finally, you include on slide 27 a CDC survey in 2002 speaking to the rates of regression. What did that survey find?

A So that's going back to the slide I presented before of the CDC, with the little orange squares. So the orange squares here document the proportion of regressive autism in each of the sites of the CDC studies.

So for instance, in Utah you have 31.6 percent of the autism sample in Utah who had a regressive course. So that's the regression state by state, as reported in the CDC study, in the official report, Table 6 can guide you. Then I was interested to look at what do we know about immunization rates in the U.S., to see if there is a relationship between regression and immunization coverage, that we should probably detect it with that particular study, which has a huge sample size, and over 2,000 children with autism.

So as you can see, the rates of regression fluctuate. And I looked, these children were born in 1994. And the CDC performs regular surveys of children aged 19 months to 35 months, where they looked at how many children, state by state, are covered by which kind of set of immunizations.

And here I just took one finding, which is complete vaccine coverage in children aged 19 to 35 months, surveyed in 1996, because that's the year, more or less, which covers the children born in 1994. And these are the rates for those children who have a full complement of immunization; therefore, between '94 and '96, so high doses of thimerosal. And so they have four DPT dose, three polio, one measle-containing

vaccines, three Hib, and three Hep-B. So they had the full complement.

And if you look at the relationship between immunization coverage with this complete set of immunizations and the reported rate of regression, this is an ecological comparison. So we should be looking at its limitation as it is. But there is clearly no relationship between the two.

So if you look at the Utah, for instance, which is the state which has the highest rate of regression, it has also the lowest, one of the lowest rates of complete immunization coverage.

The next state, which is West Virginia, has a low immunization coverage, and a lower rate of regression. If you look at states which have high coverage, like South Carolina, the rate of regression is actually under 20 percent. So as you can see visually there is no relationship between the two, and if you actually did a statistical analysis -- which is simple, looking at the nonparametric correlation between these two rates. And there is no significant relationship, of course. But you can visually assess and appreciate it.

Q Doctor, I'd like to turn briefly to the testimony and report presented by Dr. Sander

Greenland. Were you present for his testimony back at the start of this litigation?

A I was.

Q You heard him testify?

A Yes, I did.

Q And have you read his report that he filed in this case?

A Yes.

Q What did you understand to be his principal argument in this litigation?

A Well, there are several aspects to his argument. Let's deal with the simple aspect.

The argument is a statistical one. So he's saying that you have done studies, they are all negative. But you cannot hold out that there might be, may be a subgroup, it might be very, very tiny, which has a unique association with the risk exposure that these studies have been examining.

And I have no problem with the calculations, the rate on his calculation. Change them, and that's fine. It's the kind of argument you can have for all situations in medicine, where for instance if you have a substance which has been used in randomized clinical trials, in four trials which are all negative; show no superiority of a placebo; you can always have someone

who comes back and says, but have you tested the substance in the subgroup which is characterized by such height, or such particular profile. And no, we didn't do it. So you cannot rule out that there is an effect of this medication in that particular subgroup. Yes, you can always say that when you have a range of negative studies.

So the point is that we agree with that, we can all agree with that. But if we are doing that in medicine, we would be always doing studies searching for putative, very rare phenotypes, and we just cannot do that. Unless we have some preliminary evidence that there might be such a subgroup.

Q On page 8 of his report, Dr. Greenland states that it's been argued that MCV, which he refers to as mercury-containing vaccines, may trigger regressive autism in a susceptible subgroup of children. And he cites the Blaxill 2004 article that appeared in the journal, Medical Hypotheses as a source of his information. Do you have an opinion as to the source of this information?

A Yes. So if he was coming with a reasonable argument, saying that there is some preliminary evidence that this subgroup has a unique specific association with thimerosal which is not found in

other children with autism, then that would be interesting.

The fact that it has not been studied, is just reflecting the fact that this hypothesis have been put forward like six months ago. So there is no reason why investigators would have studied it before, because there was actually no idea, even at the beginning of data, to suggest that it should be studied.

So I think you cannot blame the research committee for having not done that, because there was no hypothesis. And when he put forward his hypothesis, which is a theoretical one, in his report, the only reference he makes to the published literature is an article by Blaxill, et al, in Medical Hypotheses. Which is for him, I think, a bit risky, because we know the quality, or lack of quality, of this journal.

And in fact, I read his article for the second time, and you find nowhere in this particular article the idea that there is a clearly regressive autism phenotype which is uniquely associated with thimerosal-containing vaccines. All the article is about the huge epidemic. It's an argument which is about thimerosal vaccines increasing the rates of

autism across the board, and there is absolutely no demonstration that this subphenotype or this phenotype is actually even argued for in that particular study.

Dr. Greenland, when he was asked during his testimony to refer to medical evidence or biological evidence, or any evidence, he said I don't know. He had no studies to offer, no other references to offer. So it's a no starter. It has never been put forward before six months before.

And he says -- and that, I think, is an important aspect of his statement -- that he keeps saying it's a prespecified hypothesis, a prespecified idea.

Q Does prespecified have a particular meaning in epidemiology?

A Yes.

Q What does that mean in epidemiology?

A Exactly what I was trying to say. When we do studies like, for instance, randomized clinical trials, because we know the difficulties when we do a study, the more we analyze the data, the more likely we are to find spurious results. This is the astrology example of Richard Peto, which is a beautiful example.

So when you do a study and you have no,

let's say you have no results, no association, no effect of a medication, you can then look at various subtypes or subgroups. So these are called post hoc subgroup analyses. You go in your data. You first assess your primary outcome that you have defined before the data collection. And then if you find nothing, you do subgroup analysis to see if there was a subgroup.

But we know the dangers of doing that, because the more you do that, the more you are likely to report a positive finding which would be spurious. Well known in statistics, well known in clinical epidemiology, well known in observational epidemiology as well.

There is one circumstance where these subgroup analyses are actually more authoritative, more accepted, is that if you have preliminary evidence that a response to a treatment, for instance, might be mitigated by a particular baseline characteristic of the subjects. So you can say I'll do a study of this drug against placebo; I'm going to look at these outcomes. But then I will do a subgroup analysis that I planned to do in advance.

It's a prespecified subgroup analysis. Because I know from existing data, published

knowledge, something which is already there substantial, that maybe this subject will have these characteristics might be actually different in terms of the response.

So if you have a preliminary body of knowledge which allows you to look at the subgroups separately, then you have a prespecified subgroup analysis. That's why you use that terminology as if there was this body of knowledge or variable to actually substantiate that this subgroup analysis, and criticize the fact that it has not been done.

Q Did Dr. Greenland have this body of evidence available to him when he used the term "prespecified" to define what he calls clearly regressive autism?

A He clearly said he had no idea. He referred to the other experts, and the other references cited in his report, his medical hypothesis. Where there was actually no reference to that particular phenotype.

Q Speaking of the term "clearly regressive autism," had you heard that term before this litigation?

A No.

Q Does it appear anywhere in the literature that you're familiar with?

A No.

Q In fact, Dr. Greenland said in his testimony that he's relying on you for his definition of clearly regressive autism. Do you agree that there is such a thing as a distinct phenotype known as clearly regressive autism?

A No. I'm fully in agreement with what Dr. Lord said before: the more we study regression, the less clear it becomes. It can occur after normal development. So I do not agree on this terminology.

And also, if he was, in all epidemiological studies you are serious about a subgroup before you actually define your subgroup, you must have a way to define it, measure it. And he gave no indication of how he could actually measure a clearly regressive phenotype. And everybody in the field who knows what we do will find it extremely difficult to measure it.

So if it's not measurable, it's not investigatable.

Q Dr. Greenland also referred to the Werner and Dawson article from 2005 as support for his term "clearly regressive autism." Did he accurately interpret that paper, Dr. Fombonne?

A No, I don't think so.

Q What does that paper say about a proposed

clearly regressive autism?

A The paper documents that it's using video analysis at 12 months of age and 24 months of age, of groups of children with early onset autism, a group who had regressed during the second year, and typical children.

And the findings are that indeed, at 12 months of age the children who were regressive looked more like the typical children on a range of developmental indicators. And that in a way gives some validity to this distinction.

On the other hand, although there are controls that neurotypical, they are also different. So he ignored one of the findings that the authors cite, which is the fact that in terms of other nonspecific behaviors called regulatory behaviors, there were significant differences, even at 12 months, between the regressive autistic children and the typical controls. So this is not, he didn't pay attention to this fact.

And then the conclusion that he drew, that 50 percent of children with autism might have this regression or would have this clear regressive phenotype is not supported by the discussion that the authors offer, when they say it is possible that the

infants with regression did have other types. And on this interview, parents of children with regression noted that their child had regulatory difficulties before the onset of autism symptoms.

There is something else. They say later that they cannot rule out the fact that the children who regressed, let's say, at 18 months, in fact became abnormal between 12 and 18 months of age. So I think he overestimates or he misuses the findings.

Q So the authors of the Werner and Dawson article even question whether or not there is indeed a phenotype, or any kids who are typically developing.

A They conclude that there are some children that regress in the second year of life, that we know, which seemed like the children, normal children are different from the early onset at 12 months of age.

But then they say we cannot know, because of our methodology, what is the developmental trajectory before they regress. They cannot affirm that at the time when they regressed, they were entirely normal still.

SPECIAL MASTER HASTINGS: Ms. Ricciardella, can you identify for the record the reference list and the page he was reading from?

MS. RICCIARDELLA: Certainly. We were

referring to page, the Werner and Dawson article, which I don't have. Do we know what the reference is?

SPECIAL MASTER VOWELL: It's down at the bottom of the page, Petitioner's Master Reference List 0046.

MS. RICCIARDELLA: Okay, thank you. And we're looking at page --

SPECIAL MASTER VOWELL: 6 of 7.

MS. RICCIARDELLA: Yes. And on the article itself, it's pages 894 and 895. Thank you.

BY MS. RICCIARDELLA:

Q Now, Doctor, Dr. Greenland, during his oral testimony in this case, he made comments about your citation of the Webb study in your report. And the Webb study has been filed as Respondent's Master List 506. Do you agree with Dr. Greenland's comments about the Webb study?

A Yes and no. He mentioned that the sample was small, with which I agree. This is not the issue.

The issue is that in that particular sample of 28 boys, there were 11 who had the regressive pattern, so if you calculate the proportion it is 39 percent, in line with what we just discussed. But the critical information here, even though it's a small sample, is that in the regressive subgroup compared to

the early onset subgroup, they found that the proportion of children who had macrocephaly by the end of the first year was similar.

So you know, it's a very small study, I'm not questioning that. But the point is that it's another indication, which is consistent across different studies, that if you look at correlates of regressive autism, that you don't find differences in terms of family history of the border autism phenotype, in terms of macrocephaly occurring before the first birthday. And then it's another argument to not look at this phenotype as being distinct in terms of its biological mechanisms and the rest.

And when he said that, I mean, I agree again with the fact that the sample is small, this is what we have, so we use what we have. But then he argued during his testimony that even if there is macrocephaly doesn't mean that thimerosal-containing vaccines do not actually act as a double hit on these children, and then precipitate autism.

So suddenly in his testimony, he was like reintroducing the fact that it's not the clearly regressive phenotype, but that it's thimerosal in general that might actually precipitate autism. So his theory changed in his argument in a way which I

think is not acceptable.

Q Dr. Greenland also made comments about your citation to the Richler study, the study that we heard about from Dr. Lord this morning. Is he accurately interpreting the Richler study, Doctor?

A No. I think what he said, and these words may be not exact, but he said in the Richler study there were 72 percent of children with regressive autism who had previous abnormalities. And then he concluded that shows that there are 28 percent who were normal before.

This is a leap. He cannot conclude that. What it shows is that in 28 percent of children who have regression, we could not document in that particular study with the too is that we have that their development was clearly abnormal before the regression.

And as you heard from Dr. Lord, it was more, better instrumentation, better retrospective assessment, or even prospective assessment of children, the proportion is likely to go up from 72 percent to close to 100 percent, according to Dr. Lord.

So I think in no way this study shows that there is 28 percent who really are clearly regressive.

Not at all. It's just that we are limited in the sensitivity of our techniques to assess previous normal development.

Q Dr. Greenland criticized your discussion of the Lainhart study, which is Petitioner's Master List 91. Do you have any comments with regard to his criticisms of your discussion of the Lainhart study?

A Yes. The Lainhart study is again another way to look at whether or not there is a distinction that could be drawn based on family history between regressive autism and nonregressive autism. So that if, again, the idea is if there is less genetic determination or more environmental mediation in the regressive phenotype, we should find lower rates of familial loading of autism broad phenotype in the regressive phenotype. So that was something that they did.

The proportion that they report in their study is 23 percent of -- no, sorry. The rate of the broader autism phenotype is 33 percent in early onset autism, and 28 percent in regressive autism.

I referred to this finding as showing that it is comparable. And he said well, I find that actually lower in the regressive autism, and I find his conclusion to be really a far stretch, because if

you actually perform a statistical test between these two proportions, they are absolutely not significantly different. Actually, the P value on the Fisher exact test is .78. So it's not even .10 or .07.

So the fact that he said well, I see a trend, I think goes against all his reasoning about the confidence intervals. It's true, the sample size is not great. But in that study, again, it shows that a similarity of proportions in the two groups, in which he certainly would not suggest that there is a major difference which has been missed.

Q Now has Dr. Greenland ever addressed the criticisms that you raised in your report about his argument?

A No. In my report I criticized his analogy with, when he says cancer is a broad category of disease, and in which we have types, like skin cancer and lung cancer.

And I said no, the analogy between skin and lung cancer, and regressive and nonregressive autism, doesn't hold true. Because again, skin cancer and lung cancer, they are cancers, but they are completely different in terms of the symptomatology, the age of onset, the epidemiology, the risk factors, the treatment, the outcomes. You can take any kind of

indicator; these are different diseases.

Whereas we don't have this evidence in regressive versus nonregressive autism. And in fact, we don't even know how to really secure a robust definition of the phenotype. And when we have looked at the differences, we don't find any differences.

And what I suggested is that in fact these are two different developmental trajectories, different modes of onset of the same condition. That's how most experts in the field would characterize or would look at regression today. It's just the onset is different. And the onset is different in lung cancer. I took this analogy in my report, where you can suddenly have lung cancer because you have suddenly a hemmorage. And then you bleed. And you were fine before, but then you discovered the lung cancer. That's rapid onset regression, if you wish. As opposed to the progressive deterioration -- fatigue, loss of weight -- which would be more like the early onset.

So these two different onsets exist in most medical disease. But we do not see these different types of onset or features of onset as characteristics of the disease which allow us to treat them as separate disease categories. This is the fallacious

argument.

Q Now Doctor, I'd like to talk now about your review of the records pertaining to the two children involved in this litigation. I'd first like to talk about Jordan King.

A Yes.

Q Did you review the medical records of Jordan King that have been filed in this case?

A Yes.

Q Did you review the videotape of Jordan King that was filed in this litigation?

A Yes.

Q Did you listen to the testimony of Mylinda King, Jordan's mother, in this litigation?

A Yes, I did.

Q In your opinion, Doctor, did Jordan's receipt of thimerosal-containing vaccines cause or contribute to his autism?

A No.

Q Do you agree with the diagnosis of autism in this case?

A Yes.

Q Is there anything different or unique about Jordan's autism than you encounter in children in your own clinical practice?

A No.

Q From your review of the evidence, would you characterize Jordan as having what Dr. Greenland terms "clearly regressive autism?"

A No. I think when I reviewed his medical record, and when I heard the testimony of his mother the other day, I think I would not disagree with the fact that this child has probably experienced a loss of skills, as we often see.

How we date that loss of skills is very difficult. As you know, there are some inconsistencies in the report which I had actually indicated. But if we take the mother indicated the other day that he was using a few words by age 12 months, I think she gave example of "shoe," "juice," as I recall, a few words. He didn't really have more than these few words.

And then he lost these words at around 18 months of age, if I recall correctly. That's when she dates the regression or the loss of skills. And it's both a loss of skills in terms of he didn't use these words any more, but also new symptoms occurred in the social domain. And also I think he was tip toe walking, so we can agree that there is a kind of change and loss of skills at around that age. And I

would not argue really what is the exact date, because it's actually very hard.

But if that child was actually using five words or more at age 12 months, there has been clearly no progression. The mother was not saying, nor in the record does it appear that this child after having initially spoken a few words progressed in his language development. That's the kind of thing that I think we, Dr. Lord explained very well, that we see sometimes skills which emerge, and then there is a plateauing of these skills which then can be followed by the loss of skills. And it's very clear to me that -- clear, I mean as far as the recorded evidence can suggest. That the language did not progress most likely normally between 12 months and 18 months of age, which is the date of loss of skill that we can record.

So I think it's likely that the development was not entirely normal before that loss of skills. But it's hard to be, it's hard to be definite about these issues, because it's all based on retrospective assessment. And when you look at the records, just the records which are prospective recalling, even of parental reports they do show a high number of inconsistencies in terms of the dates. And that's

something that we know well.

Q And speaking of the records, are the pediatric records an accurate and reliable measure of normal development the first 12 to 15 months of life? Not just in Jordan, but in all children who are later diagnosed with autism.

A No, it's not a tool that you would use to detect. It depends, I think we should characterize what is in the records, what we all mostly find is that the records are empty, up to a point where it seems to seem very significant.

So if they miss a lot of the early symptoms in their examinations, and they are not documented well in the record. However, when there is a documentation of symptoms in the record, then usually it's a valid observation. It's not sensitive. Specific, but not sensitive.

Q Are pediatricians adept at recognizing subtle signs of autism during the first 12 months of life?

A No, I think they are not. I mean, the first 12 months of life, it's actually very difficult for everyone. There are new guidelines which have been offered by the American Academy of Pediatrics last fall to really promote systematic detection of

autistic symptoms in young children by pediatricians. So I think it's coming.

But at this point in time, in most areas which I know, there is still a lack of expertise by general practitioners, family doctors and pediatricians, to detect autism. And that's why we have this unfortunate lag in most studies between parents becoming aware of the symptoms or that something is not right in their child, usually at 18 months of age or around that age. And then there is a delay before the child is referred and then diagnosed, which is too long. And then we are aiming at reducing by our education.

Q Doctor, in your report you state that it's impossible to draw any conclusions about the efficacy of the various supplements and treatments that Jordan, that comprised Jordan's treatment program. Can you please explain what you mean by that?

A Well, when the diagnosis was made, understandably -- and that's what I see in my practice all the time -- parents are looking for interventions. And they usually do engage simultaneously in different types of interventions.

So in the case of Jordan King, I don't find in front of me the exact -- I think he started to do

speech therapy, and there was a form of applied behavioral analysis, which has a behavior intervention which was put in place. And at the same time, some more biomedical treatment of the diet or other kinds of supplementations were implemented.

So it's a situation where you have multiple treatments which are initiated by different people, who often do not talk to each other, often. And when there is a change in the child, it's absolutely impossible to ascribe the change in that child to any particular treatment intervention, because you cannot disentangle the effect of one, as opposed to the effect of the other, and you cannot disentangle the effects of intervention from the effect of natural history. Because some of these children do progress naturally, even in the absence of intervention.

So I think we cannot really, based on this treatment record, draw any causal inferences about which did what to his outcome.

Q Now I'd like to turn to the case of William Mead.

SPECIAL MASTER HASTINGS: Ms. Ricciardella, before we leave the Jordan King case, let me just ask one question about the last answer of Dr. Fombonne.

You described there generally, Doctor, how,

when there's a lot of different treatments going on at the same time, one can't draw any causal inferences from any improvement or a lack thereof.

Now, is that true of Jordan's specific case, that he had a lot of --

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: Are you saying that applies to Jordan's individual case? He had a number of --

THE WITNESS: Yes, yes. I'm saying that about him as a specific child.

SPECIAL MASTER HASTINGS: Okay. Thank you, Ms. Ricciardella.

MS. RICCIARDELLA: Certainly. I'd like to turn to William Mead.

BY MS. RICCIARDELLA:

Q Same questions. Did you review the medical records of William Mead that have been filed in this case?

A Yes.

Q Did you review the videotape of William Mead that was filed?

A Yes.

Q Did you listen to the testimony of George Mead, William's father, in this litigation?

A Yes, I did.

Q In your opinion, did William's receipt of thimerosal-containing vaccines cause or contribute to his autism?

A No.

Q Do you agree with the diagnosis of autism in this case?

A Yes, yes.

Q Is there anything unique or different about William's autism than what you encounter in your clinical practice?

A No. He's one of the child that I see often in my practice. And I was pleased to hear from his father that there were progresses made by William. And although his language is still not functional, as the father put it, it's still progressing very well. So it was nice to hear.

Q And from your review of the record and the other evidence in this case, could you characterize that William has clearly regressive autism? Again, as defined by Petitioner's experts.

A No, I cannot say that. Again, pretty much like for the other child, I would agree that there is a pattern of loss of skills, which is credible in this case, particularly in terms of his language. But I

found it very difficult to document exactly the timing of regression, and to assess what happened before the regression occurred. I think I -- okay, yes.

Q Go ahead.

A No, I was thinking back to Jordan. I'll come back to it later.

Q Now, Dr. Mumper testified that when William was treated for a chronic condition caused by mercury by way of chelation, he improved. And therefore, she concludes that thimerosal-containing vaccines are a possible environmental factor that must be included on William's differential diagnosis. Do you agree with that line of thinking?

A There are multiple aspects to your question. The line of thinking, do I agree with it. I think again it's a situation where when you even listen to the testimony of Mr. George Mead last time, it was clear that when he was diagnosed, the parents, as usual, looked for immediate treatments and intervention.

They embarked immediately in the glutein-free casein-free diet, while at the same time there was also behavioral intervention which was started, and different supplements and different interventions were provided to William in sequences which again do

not allow us to draw meaningful causal inferences about what changed in that boy, and what does what.

And in particular, I would say that if you look at the treatment by Dr. Green, there are notes about William where he says progress, progress, progress, progress, progress. And then at the end there is no progress.

So you really wonder how the treaters do really assess change. So it's a question which I ask myself in my practice. But we have tools that we can sometimes use to evaluate the improvement as a function of our intervention, but none of that was really used in this particular case. So it's very hard to make sense of the behavioral improvements, and where they come from, and what was driving the change of the treatment from session to session. I think it's a mixture of different interventions which are striking for the fact that most of them lack evidence for their efficacy.

Q The treatment of chelation, Dr. Mumper says that she believes that it, William improved by virtue of chelation; therefore, thimerosal in vaccines must be included as a potential environmental factor on his differential diagnosis. Do you have any opinions with regard to the efficacy of chelation?

A No, there is no evidence for the efficacy of chelation therapy at all which is published. There is no reason why you're actually even anecdotally embarking on chelation therapy as a professional. It's not part of any guidelines to treat autistic children by professional bodies.

Q Dr. Mumper also testified that William benefitted from secretin as part of his treatment for, specifically for pancreatic enzymes. And she testified that secretin has been shown to restore neurodevelopment. Do you agree?

A No, I do not agree on that. And secretin has been shown to actually have no efficacy in autism, despite a huge enthusiasm for the compound in the mid-nineties when this compound was put to a critical test using the method that we use in medicine to look at efficacy of intervention, which is the randomized clinical trials.

Three separate randomized clinical trials showed all that secretin did not differ from placebo in terms of efficacy. So I think we have actually evidence for secretin that we don't have for chelation therapy, but evidence that it doesn't work.

So the anecdote that Dr. Buie giving a secretin injection was followed by an improvement in

William, it's an anecdote. I am not disputing that observation; I'm simply observing that if, as Mr. Mead said, it was actually one of the times that William was actually more, I don't recall the adjective that he used, but he said more present or something like that. If that was the case, why it was not pursued as a treatment.

So I think these are part of the difficult aspects of the parents who have children with autism. They try to do multiple things, and we understand why. When you do things, you often observe things which follows and you make correlations or connections that will not be sustained or observed if you have a rigorous experiment.

Q And is your opinion with regard to the various treatments that comprised William's program the same as it was for Jordan King, about having a hard time picking out one as being efficacious?

A Yes.

Q Does it apply to William, as well?

A Yes.

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

SPECIAL MASTER VOWELL: Well, given the timeframe, it would be an appropriate time to take a

lunch recess. So why don't we reconvene at five to?

(Whereupon, at 12:55 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 1:55 p.m. this same day, Wednesday, May 28, 2008.)

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

(1:55 p.m.)

SPECIAL MASTER VOWELL: We're back on the record. Dr. Fombonne is on the witness stand. And you may begin your cross, Mr. Williams.

MR. WILLIAMS: Thank you, Special Master.

Whereupon,

ERIC FOMBONNE, MD

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

CROSS-EXAMINATION

BY MR. WILLIAMS:

Q Good afternoon, Dr. Fombonne.

A Good afternoon.

Q I am Michael Williams, representing the Petitioners' Steering Committee. I am going to cross-examine you about the general causation issues, and then my partner, Tom Powers, is going to cross-examine you about those individual case issues.

Where I'd like to start is to try to get your best estimate of the current true prevalence of autism. And we can start by looking at paragraph 64 of your report. Do you have your report handy?

A Yes.

Q We'll put it up on the screen. It's page 25.

A Yes.

Q And if you blow up the first half of the paragraph, Scott, or highlight it, it would be good. Actually what I want you to highlight is the conservative estimates sentence.

Now, Dr. Fombonne, in this paragraph you provide a breakdown of the prevalence rates for four different subtypes of pervasive development disorder, or what we've been calling ASD in this trial, correct?

A Yes.

Q And you estimate that for autistic disorder itself, it's 13 per 10,000; for PDDNOS, and that's pervasive developmental disorder not otherwise, what's the S stand for?

A Otherwise specified.

Q Not otherwise specified. That's 20.8 per 10,000. For Asperger it is 2.6 per 10,000, and for childhood disintegrative disorder, 0.2 per 10,000.

Now, those add up, you say, to a conservative estimate of 36.6 per 10,000. But then you go on to update that with more recent studies, and what I want to ask -- and that's where you come up with your, on slide 7, your 66 per 10,000. That's a

fair summary of what your views are?

A What's the question exactly?

Q The question is --

A Oh, on this slide, yes.

Q -- when you say six recent epidemiological surveys yielded higher rates, in the 60- to 70-per-10,000 range, you provided a slide that said it was 66.

A Yes.

Q That's your current best estimate of the current prevalence, right?

A Yes, 66, 70, 65. I used in that slide the estimate from the CDC because it's relevant to the U.S. and it's actually consistent with most recent surveys. Or so I think it's a reasonable figure. I don't think it has to be taken as an absolute truth.

Q Right. When you give decimal-point precisions of 20.8 per 10,000, are you confident about those decimal points?

A No.

Q No?

A I mean, you have to understand the method by which I arrived at these estimates. These first very conservative estimates are based on a review of all published studies, of which I've looked at the most

recently published surveys over the last 15 years. And I aggragated them to get average estimate of the prevalence of each subtype of PDD. So it's a method which is, you could criticize, and I'm not looking at it as absolutely perfect. It was a starting point.

And this is really averaging studies, which are very different in designs and methods, so I know it's a kind of mixing a bit apples and oranges. So that was what we had up to the late nineties. We had studies which were very different.

Then the next statement is looking at studies which have been published since about 2000, where new methods were developed, and more precise case finding methods were used across different populations, more precise case definitions were used, tools to match the case definitions were modern this time. So there was a new generation of study, if you want, which started in England, and also in the U.S. And then now most studies which have used similar kinds of methods are giving a range of estimates, but the range which is the most attractive, if you wish, is between 60 to 70 today.

I'm sorry, and the two CDC surveys, the survey done on the children born in the U.S. in 1992 and the other survey on children born in 1994 were all

surveyed at age eight, provided within the U.S. two highly consistent estimates of 66 and 67, I think, per 10,000. And then the calculations are using the CDC estimate, because it's natural to do that.

Q Let me suggest that we -- I'm going to try to ask questions that don't require really long answers.

A I'm sorry.

Q And you know, if you need to explain something, you will get a chance on redirect to do that. But let me show you a slide I prepared, because I want to now unpack this just a little bit with you.

Now, this is a slide that we prepared. And this has your totals that we've already gone through from paragraph 64 on the left side, that added up to 36.6; but in your report you don't give a breakdown of the prevalence rates for the four subtypes. And I wonder, do you have an estimate for those subtypes within your overall number of 66?

A No, no. It depends which study you take. But for instance, the CDC surveys have not separated out children with autistic disorder and children with PDDNOS, which both conditions fall in the bulk of the cases.

So we cannot really, from these particular

surveys, derive estimates for autistic disorder or PDDNOS. So that's one aspect.

Secondly, in other surveys where it has been done, it seems that the results of studies are consistent for the overall estimate of the prevalence of the combined formal types of PDDs. But where people draw the line between autism and PDDNOS seems to be less reliable. So that would be more difficult to do based on recent surveys.

Q Well, do you have an estimate of what would go in those boxes? Or are you just saying you don't know what would go in those boxes?

A I have estimates in my own study, but they, in other studies they are different.

Q Do you think that the proportions that were present in the earlier survey would stay roughly the same?

A They tend to be, they tend to be more or less like these in most studies, but not all of them.

Q Well, is there any one of those that you've known has changed in proportion, from what it was in the first number?

A No. CDD is still extremely rare. Autistic disorder, probably the recent surveys would be 20, 22. In most studies PDDNOS is more like 30, 34, 35.

Asperger is a kind of a very elusive phenotype, which I think is unlikely to persist in the next classification. And CDD is extremely rare.

Q All right. Well, we'll leave the question marks there then for now.

Now, you believe that this estimate of 60 to 70 per 10,000 for the entire spectrum, that that rate is true not just of the United States, but also of Canada, right?

A That's the rate we had -- yes, in my survey which I published two years ago, we had a rate of 65 per 10,000.

Q And also in Europe?

A I mean, there are new studies which are in progress, which show rates which are sometimes higher, sometimes slightly lower. And you have to look at the methods used in each survey to interpret this viability and estimates.

Q Do you have any reason to think that the prevalence rate of the total spectrum of ASD is different in Europe than it is in North America?

A No.

Q No. What about the rest of the world? Is it roughly the same around the world?

A It's a difficult question to answer. But

from what we know, firstly we find autism in most countries when it has been surveyed. There are now rates in Japan which are very high. They were high before, but there are new studies coming up which show higher rates.

There are new studies in England showing higher rates as well. So there are studies showing higher rates, and others which show somewhat lower rates in this range I gave. So it's going to, it's likely to change as the, in the next five to 10 years.

The reason is that if you look at the slide of the CDC, you know, you have this high rate, for instance, in one percent in New Jersey. In Alabama it's like a third of that.

Now, it's supposed to, on the average is 66, okay. So the average is an average. So if the CDC goes back in the field in 10 years from now, hopefully in Alabama there will be more services, more awareness, and the case finding in Alabama will be more efficient, so it will not decrease in New Jersey. So it's very likely that this average is likely to go up not as a function of change in the incidence but improvement in case ascertainment.

Q Well, do you have any current estimate of what the true prevalence rate is then in the United

States? Not just what these imperfect studies have shown so far. Do you think it's higher than 66 per 10,000?

A No, I don't think it is. I don't know.

Q Well, I thought you just explained that you expect Alabama to come up, and New Jersey not to come down. Won't that raise the overall prevalence rate above 66?

A Yes. It will not be surprising that the, again, within the methodology of the CDC in the future, they would show higher average estimates for the U.S. But how much higher, I don't know.

Q Okay. Now, do you think that this prevalence of the entire spectrum has been the same for the last 20 or 30 years in this country? No significant change in the true prevalence rate?

A You have to explain to me what is a true prevalence rate because when we do a survey, we have an estimate, an estimation. That's what we found, that's the estimate. The estimate is meant to tell us something about the true barometer in the underlying population. So the true barometer we never know. So it depends on the bias and the precision which is attached to our estimate.

Q I understand.

A Do I know the true prevalence rates now or in the past? No, I never know. I rely on estimates.

Q But you do believe the true rate now is probably higher than 66 per 10,000.

A It may be slightly higher, yes. It's possible.

Q Well, do you think that it has increased in the last 20 years? The true prevalence rate in the United States?

A It's hard, you know, it's hard to evaluate these questions. That's a question about trends over time. So if you are asking the questions why current estimates of PDDs seem to be higher than the rates which were published 20 years ago, for instance in the UCLA Utah survey --

Q I'm not asking you what the studies show, because I know you think that those studies failed to ascertain all the cases. And they didn't have the same broad diagnostic criteria that we now use. So they were more of an underestimate then than the one today.

A Yes.

Q What I'm trying to get at is, is it your concept of this disease that its prevalence rate has essentially stayed unchanged? However difficult it is

to measure that, has the prevalence rate essentially stayed unchanged for the last 20 or 30 years?

A I don't know. I always I think said in what I write on these questions that one of the major reasons for the increase in the prevalence estimates which have to do with the broadening of the concepts, the change in diagnostic criteria, improved awareness, better case findings. So we know that all these factors could account for a large proportion of the increase, and maybe all the proportion. I know we cannot really be sure about that.

But it's still an open question as to whether or not what I would call the true incidence rate in the population has actually also gone up to a some extent. That we cannot rule out, or in, that it's the case.

Q In your report you actually describe some, what you claim are cases of autism from historical examples, hundreds of years ago, right?

A Yes.

Q Do you think that the true prevalence rate was the same several hundred years ago as it is today?

A I don't know. It's a very, it's very hard to address this question. I have not done the historical studies. There were probably many children

who were autistic, and not recognized as such.

And as in today's populations in developed countries, there are many adults who are undiagnosed. That's what we know. I run an adult clinic; I can tell you that I am referred very regularly usually high-functioning autistic individuals who have a typical history of autism and have not been diagnosed.

So your question is a good question. It's very hard to address it with data. So I don't know what was the true prevalence.

Q Let me take you back through evolution. Has there ever been any assessment of autism in primates? I mean, is there any hint at all that primates other than humans have ASD?

A I don't think it would be -- primates do not have autism, so it would be difficult to evaluate that.

Q Primates are subject to virtually all of our other diseases, aren't they?

A I don't know that.

Q Okay. Then let's talk about the relationship between prevalence and incidence.

If the prevalence rate is staying relatively steady over time, does that mean that the incidence rate needs to stay steady over time, also? In other

words, if you don't have a change in prevalence, can you have an increase in incidence anyway?

A It depends on several factors, like mortality, for instance. And this is a life-long handicap, so you would expect that people who have the disease stay in the population, and that the prevalence stays the same.

Now, if they die from their disease, it might, the prevalence might decrease as a function of that, with age, for instance. Even with incidence being constant. There is some evidence that mortality rates are slightly increased in autism like twice or three times.

But other than that, yes. If the prevalence is stable, you would assume that there is a constant incidence rate.

Q And if we confine ourselves to children under age 20, as you have in slide 7, you give an estimate of the number of U.S. children under age 20 who meet the ASD criteria. As each birth cohort graduates to age 21, if the incidence rate is staying, if the prevalence rate is staying the same, you would expect that the new birth cohort coming in will have the same incidence rate, right?

A The same prevalence or incidence?

Q If the prevalence rate of under 20 years old in the, let's call them children under 20.

A Okay.

Q If that stage has stayed the same for the last 10 or 20 years, wouldn't the incidence rate in that group also have had to stay the same?

A Yes, probably.

Q Okay. And is the incidence rate also, then, 66 per 10,000?

A No, that's not the way you calculate the incidence rate.

Q I can't hear you, I'm sorry.

A No, it's not the way you calculate an incidence rate. You have to have different measures to calculate incidence. It depends which kind of incidence you are talking about. Incidence are referred to person years as a denominator, so it's more complex than that.

Q Well, let's talk about newly diagnosed cases. If the prevalence rate in the 20-year-olds is 66 per 10,000, and then they all become 21, don't you, in order to keep the prevalence rate the same in that next year's group of under 20, you would have to have just as many new diagnoses of autism in order to replace the ones that just became 21, wouldn't you?

A You mean in the 20-year-old cohort?
Q Yes.
A Yes, yes.
Q Okay. Now, when you calculate that the prevalence is one child in 150, are you counting the one-year-olds and two-year-olds in that population?
A No. You don't have to. This is based on the CDC surveys, which are only looking at children aged eight. So it means that in children aged eight today in the U.S., based on the study, one child, aged eight, out of 150 has an ASD.
Q Okay. And you believe that the age-specific prevalence rate at age eight has stayed relatively steady for the last 20 years or so.
A Not the prevalence rate, no. Because it has, again, there wasn't ascertainment in the past. So if you look at age-specific, like an eight-year-old, 20 years ago you would have a lower prevalence rate.
Q As to whether or not there has been an epidemic of ASD in this country over the last 20 years, it's your opinion that there is no good evidence of that, right?
A No. There is, I think no one can really affirm that there has been an epidemic in the sense of

an increasing incidence of autism or ASD. The prevalence has increased, there is no doubt about that. But it's reflecting the factors which I described before, and we don't know if in addition to these factors, which have to do with how we conceptualize and diagnose the phenotype and how we identify cases, we do not know if in addition to that, there might be also the contribution of a real change in the incidence of the condition. That's an important question. It's an important question. But there is no definite answer on that.

Q And I think Dr. Rutter agreed with you yesterday. Let me try to see if I can say this precisely for you.

You and Dr. Rutter seem to both believe that there is no good evidence of any increase in prevalence or incidence of the entire spectrum, but you don't know whether there was an increase. You just don't think there is any evidence for that. Is that a fair summary of your view?

A Yes, except that I need to qualify what you said. It's not about prevalence, it's about incidence, okay? We all agree that there has been an increase in the prevalence. The real question, I think, behind the epidemic hypothesis is whether or

not there has been an increase in the incidence of the disorder.

And for that, yes, we all agree that the evidence, there is no positive evidence to support that at this point in time. It doesn't mean that it's not happening. We cannot rule that out. So it's an important question which remains to be studied.

Q Now, we have heard some of the experts, even for the defense, agree that there have been some cases of autism probably induced by things like rubella infections in Mama, by thalidomide given to pregnant women; perhaps by terbutaline given to pregnant women.

Do you think that the number, the absolute number of those cases that at least were purportedly induced by these environmental factors, would they be so small that they would not show up in any of the measures, for instance, for prevalence that we have?

A Clearly, the risk attached to these exposures is maybe high. In relation to thalidomide, I think the risk ratios or odds ratios of 20 or 30 have been reported, or even higher than that.

But even if the strength of the association is high, you have to factor in the prevalence of the exposure. And because these exposures are extremely rare, the proportion of cases which is attributable to

these rare exposures is extremely low.

Q Absolute number is very small.

A Yes. Another way to put it, if you take 1,000 children with a PDD diagnosis, it's only a handful of them who would have had their autism through these rare exposures. That's what we could conclude.

Q And any increase caused by those small numbers would be lost in the statistical noise of the measurement of the overall prevalence, right?

A Probably.

Q Now, in 1997 you published a prevalence study that I want to discuss with you just briefly. This is RML-149. It's a DOJ Exhibit. I have a copy to give you.

A Thank you.

(Pause.)

Q If we could put the title and the abstract up. Now, this is a survey that you did. It says the objective was to estimate the prevalence of autism. And that was one of your objectives in this paper, right?

A Yes.

Q And then in the results section of the abstract, if you could highlight the sentence, Scott,

that says the prevalence rate was? That's all.

Now, when you did this prevalence study back in 1997, when you counted all the pervasive developmental disorders, you only got a prevalence of 16.3 per 10,000, right?

A Yes.

Q And that included all four of the categories we talked about.

A No.

Q No? Which ones did you leave out?

A Yes and no, yes and no. You have to understand the methods used in this survey. It was based on children who were school-age basically, and identified in their local educational authority as having special needs. So that at the time in France, and these children were born between 1976 and 1985. So we are going back 30 years now in history.

And so these are children who are referred usually by local psychiatric teams or schools, but mostly psychiatric teams, to get support in the school system. And at the time, awareness in France about autism was extremely minimal, and there is still actually I think --

Q Well, is it fair to say that when you did this survey and published it, that you, because of

your limitations on methods, you greatly underestimated the prevalence rate, didn't you?

A Probably, because there are many children who were autistic, high-functioning with language, who were not easily identified in our survey. So yes, it would probably have been an underestimate of the true population rate. But that's, most surveys, by definition, provide underestimates of the true population rate in that field of research, so it's not a surprise. But it was still at the time an estimate which was actually surprisingly high, considering the context in France.

Q But don't you think that if you surveyed that same group of kids, and had had DSM-IV and the ascertainment awareness that we have today, you would have gotten a much higher prevalence?

A Yes. Yes, absolutely.

Q Probably as high as 66 per 10,000.

A I don't know.

Q Now let's turn to your discussion of time trends. You have a section of your paper -- I mean your report, excuse me. I want to start with paragraph 68 if we can of your report. That's on page 26.

You say the time trends and rates can only

be gauged in investigations that hold these parameters under strict control. And I think by parameters, you're talking about case definition and case ascertainment, correct?

A Yes, correct.

Q Then you say, "This was achieved only in a handful of studies." What studies are you talking about in that sentence, the handful of studies?

A In writing that I had in mind the time trend analysis that was published in the paper that you just mentioned before. That was the first time that there was an examination of time trends in the prevalence of autism in the French surveys.

When I pooled together the results of different surveys in birth cohorts from 1971 to 1985, and I looked at trends to see if there was evidence of an increase or not, it could be interpreted more meaningfully because I pooled together three different surveys which employed the same case definition and the same method. So that's one of the studies which could do that.

Q You said, you used the plural, though. I just wondered what, aside from your own 1997 study, what other studies are you talking about in this sentence?

A Other studies than this one?

Q Yes. Well, you say there's a handful of them. I assume you mean more than one.

A Okay, yes. Okay, let me go on.

Q Which ones are they?

A The studies that we've done in England with my colleague, Chakrabarti, where we published first a survey in 2001 in a given area of the Midlands in the UK, on children born 1992 to 1995. And when that was completed, we, because we had an opportunity to do a repeat survey with the same approach in the same area, so the methods were the same, the case assessment was the same, we repeated a survey in children born in subsequent years. And we found that the rates were similar; there was no difference. So it was a small time interval, but by holding the methods constant, there was at least, within those years, no evidence for an increase.

Q Were you looking at the full spectrum of all four types of ASD?

A Yes, yes.

Q And what was the prevalence rate that you found in those two time periods?

A If I recall, it was a 63.6 in the first survey, and 59-point-something in the second one.

Q So more along the lines of what Dr. Rutter called our modern numbers.

A Yes.

Q Right, okay. Now, the next sentence in the same paragraph says, "In addition, factors such as development of services and support systems for children with autism," and we go to the next page, "improved awareness by both professionals and laypersons, decreasing age of diagnosis, availability of information from the internet, parent support groups, and the removal of the stigma, have all contributed to the increasing rates of diagnosed ASD." And you believe that to be true.

A Yes, I do.

Q In fact, you believe that those factors explain the apparent increase in prevalence rates over time.

A Contribute to the apparent increase, in a significant way.

Q Is there any other factor that you're aware of that contributes to the apparent increase in prevalence that you haven't enumerated in this paragraph?

A Let me see. Yes. I would think, for instance, that change in the educational system, the

availability since the late eighties, early nineties of behavioral interventions, the efficacy of which was first demonstrated at that time, has changed dramatically the likelihood that a child would earn a diagnosis of ASD, as opposed to a language disorder, or as opposed to mental retardation.

Q Now, you then say that, "A few approaches have been employed to evaluate time trends and rates of autism." And you give three categories: referral statistics, comparison of prevalence studies, and incidence studies.

Then I want to turn our attention to the referral studies. You use as an example the California Department of Developmental Services, don't you?

A Yes.

Q And in the California Department of Developmental Services statistics, there has been an increase over time in the prevalence, or excuse me, in the incidence of autism, right?

A Prevalence is okay.

Q What?

A Prevalence is fine.

Q Prevalence is fine?

A Yes, yes.

Q Okay. There has been an increase in prevalence.

A Yes.

Q And you believe that that is a result of these types of changes in sort of the social milieu, not in the underlying disease.

A Yes. I mean, I assume that a large proportion of that increase is due to these factors which are listed, as opposed to an increase in the incidence. And the demonstration of that, if you want to look at the Schechter and Grether paper, which I referred to this morning, where they show that -- I think I would need to have the paper maybe.

Q If you give me the number, we could probably put it up on the screen.

A But the idea is that in that database in California today, the peak of prevalence --

Q What's the exhibit number on that, if you could let me know? Okay. I can't read it.

(Discussion held off the record.)

Q This is Petitioner's Master Reference 432.

A So if you look at figure 1.

Q Yes? Figure 1 is on page 3 of the exhibit.

A Yes. And if you look at the highest prevalence figure in that study, it is in the children

who are aged six. And in the text on the same page, in the right-hand column, it says, in the middle paragraph, the highest estimated prevalence at 4.5 cases per 1,000 live births was reached in 2006 for children aged six years and born in 2000.

So it's just to illustrate the fact that in the recent analysis of this DDS database, the highest prevalence that they have is for children aged six. And that prevalence is 45 per 10,000; i.e., lower than the, what you would expect from the CDC population-based surveys.

That's why these administrative databases tend to underreport, and are not good tools to estimate population prevalence.

Q Well, and it's not just that they underreport. At any point in time, if you go back to the earlier years, if you go back to, let's say, what's the earliest time we have six-year-olds in there? I guess 1992, right?

A I'm sorry, I can't see. No, you can --

Q The six-year-olds are the dark diamonds, aren't they?

A Yes, they are. 1991. No, sorry, 1992, you're right. Yes.

Q And what is the prevalence rate in those

years? What did they have in this database?

A It seems to be around 15.

Q And you believe that that's an even greater underestimate of what the true rate was, right?

A Yes, yes.

Q Okay.

A Well, you just have to take current figures, and then calibrate them against the CDC surveys. And you see that these figures are lower in the administrative database as compared to population survey estimates. That's all that it means.

So even if it goes up again in this particular birth cohort, it doesn't mean that the incidence is increasing. It's more a catching-up type of phenomenon.

Q Right. And if we go back to his report, on page 28, at the end of paragraph 70 at the top there, I just want to get the last sentence. You summarized this point you've been making about the California DDS system and other referral systems by saying that, "Evidence from these referral statistics is very weak, and it cannot be used to determine changes in the incidence of the disorder." And that's your opinion, right?

A Yes, in the incidence, certainly. But the

choice of terms is very precise here. It's to evaluate changes in the incidence.

(Pause.)

Q If we now go to paragraph 82 of his report, which is on page 32. You summarized your whole discussion of these time-trend studies by saying that, "The available epidemiological evidence does not support the hypothesis that the incidence of autism has increased, for reasons other than changes in diagnostic practices and improved detection."

That is still your opinion, right? There's no reason to think these trends are going up in time, other than for those two reasons.

A Again, it's an hypothesis which cannot be ruled out, and needs to be examined. But if you review existing surveys, you cannot really demonstrate that there has been an increase in the incidence. That's what it means.

Q And at the bottom of this paragraph you say, "Most of the existing epidemiological data are inadequate to test properly hypotheses on changes in the incidence of autism in human populations. The studies that could more adequately control for alternative explanations have failed to detect an upper trend in rates of ASDs."

When you say the studies that could more adequately control, you're referring to your studies?

A The handful of studies, yes.

Q The same handful.

A Yes, the same handful. It is because it is striking that when you actually perform comparisons over time, when you can actually maintain somewhat constant the case definition, then the trend up that you see usually disappears. So it's quite, it's quite striking.

But it doesn't rule out, again, that there might be a change in the incidence.

Q It's possible there's some increase in incidence, but we just don't have the information to tell us for sure.

A Yes, yes. Exactly.

Q If there has been an increase in incidence, though, you think it's been pretty small, don't you?

A Yes. Probably. If there is such a phenomenon, it does not account for most of the increased numbers of diagnosed children. That must account for some of a small proportion of it probably.

Q Well, now what I'd like to do is go to your analysis of the studies on time trends and incidence with respect to thimerosal-containing vaccines. Let's

start with the Schechter-Grether paper, the most recent one.

(Discussion held off the record.)

Q You showed, in your slide --

SPECIAL MASTER HASTINGS: Can you identify that in the reference list?

MR. WILLIAMS: Yes. This is, again, Petitioners' Reference Master List 432. And we're going to be discussing figure 3, which was also on his slide 17.

Can you pull up the one in the paper, since I don't have a copy of his slide to blow up?

BY MR. WILLIAMS:

Q Now, I thought you were suggesting that this trend line provided evidence against the theory that thimerosal-containing vaccines caused an increase in incidence. Weren't you trying to do that?

A Yes. Could you repeat the question? Maybe I didn't understand.

Q Yes. I thought, despite the fact that we've just gone through that you said the California DDS data are not a reliable indicator of changes in incidence, I thought when you showed this slide you were suggesting that this chart actually does provide such evidence; that the incidence rate is increasing

for real, over here in this part where you have the red line.

A Which is the red line? I don't have this line. Oh, yes.

So the point is that if you look at the, these are for children agred three to five, okay? And you can see that quarter after quarter in this dataset, there is a regular increase in the numbers we are reporting, okay?

Q Right. But let's look at, let's start with the back of this line, back in 1995, quarter one. Where on your slide you have 0.6.

A Yes.

Q That 0.6 represents six per 10,000, right?

A Yes.

Q And you just finished telling us that six per 10,000 is probably a tenfold underestimate of what the real rate was.

A Yes.

Q So if the real rate -- and this chart only goes up to, well, if it was really six, it would be way up here on this part of your chart, wouldn't it? It wouldn't be down at six per 10,000; it would be up here at around 60 per 10,000.

A Well, I think the scale is per thousand.

Q Okay, per thousand. That's what, I'm pointing at the six, the number six. Yes, there's a red arrow there that my assistant has put.

Isn't that where you think the probable real prevalence was in 1995 in California? At where that red arrow is.

A Oh, I see what you mean. Your true prevalence rate, right? That's what you're -- are you trying to say that what I'm thinking is that it should be six?

Q Yes. Didn't you just --

A Per thousand.

Q -- finish saying that you thought that the early numbers in California in this referral database were a gross underestimate of the real rate?

A Yes, probably.

Q And so probably it was around six or seven per thousand then, right?

A I don't know that, but yes.

Q But that's the most probable, isn't it?

A Yes, probably.

Q And so then this trend line --

A I would like to actually qualify that, because we are here talking about rates in three- to five-year-olds, okay? So the rates of 60 to 70 from

the CDC applies to children who were aged eight, where they have shown in their previous survey that it's the age where ascertainment is better, and the prevalence is probably better estimated in that age group.

So if you were to look at birth cohort children age three or four or five, by definition the rates, if you do a prevalence survey, the rate would be lower than that, because of the age of diagnosis is still like four or --

Q Okay. Well, if we know that in 2007, the first quarter, the rate was just over four per 10,000, right?

A In which --

Q This number, 4.1.

A Yes, yes.

Q And you think that the real background rate has essentially stayed the same all this time, between 1995 and 2007.

A Probably.

Q Probably. So a real picture of this graph would have essentially a straight line going across from four or five over to here, wouldn't it? Like Scott just put on the graph. Isn't that more probably the reality in California?

A I don't know. That's an hypothesis, yes.

But we have to deal with what we see and what we can estimate. Yes, theoretically you're right to say that.

Q Well, let me ask it this way. Do you think that the California referral database figure of 0.6 per 1,000, or six per 10,000, do you think that is a reliable estimate of the true rate of autism in California in 1995?

A No.

Q Well then, how can you offer it as evidence in favor of your claim that thimerosal has nothing to do with an increase in incidence?

A Because I think you are confounding two things. One, your argument is about looking at what is a real estimate; is it underestimation, overestimation, what is the truth. That is about estimating the prevalence rate in the population.

Now we are talking about trends. So if you look at trends, you can look at factors which explain trends even in a situation where you have underascertainment, if the underascertainment remains constant, of course.

Q But I also understood you to say just a few minutes ago that the entire increase in this trend in the California database could be explained by better

case ascertainments, and better diagnostics, or broader diagnostics, right?

A Yes. Yes.

Q So if that's true, and the most probable background rate is this red line, this graph doesn't provide any evidence one way or the other about thimerosal in vaccines, does it?

A Of course, yes, it does. You have a trend, which is going up, which reflects in the DDS system improved awareness, better referrals, improved access to services. And that is the underlying trend which is going up.

Now, if you have in disease causation, a risk factor which disappears at one point in time, you might keep your trend, but it should go down like this. You should have a decrease when you save, you know -- some cases of the disease do not appear any longer because the exposure has been removed.

So what you should see is that, for you, is that an increase like that, when thimerosal is removed, you should see a decrease, there should be a decrease, and then the trend can continue otherwise. That's what you are testing for.

Q How big an effect would thimerosal have to have to make an effect on this line?

A Well, it seems that it has no effect, because the trend has not changed.

Q Yes, but there is statistical noise in that line, isn't there?

A Yes, but it's pretty robust, because you have multiple data points. And in fact the trend continues, and actually accelerates slightly. So there is, if there was a strong effect of thimerosal, it should have been seen.

And even if it applies to only a proportion of the cases of autism, it should be seen, if only because if you look at the absolute numbers, in California every year they add about 3,000 new cases.

So let's argue for the time being that thimerosal accounts for half of the cases of autism. Let's hypothesize, we'll hypothesize. So you should certainly see the trend continuing, but you should have certainly a decrease by 50 percent of your level. The trend might continue to reflect other factors, apparently.

Q But what if autism, what if thimerosal is only inducing one third of the regressive cases? Say, and be generous with how much regression is here, let's pick the 20-percent number. If thimerosal is only inducing one third of those regressive cases,

that would only be a six- or seven-percent difference.

Are you saying that this is still statistically powerful enough to see that?

A Probably. You would see it. On 3,000 cases it would be something like 200 cases less per year that would be seen.

Q Okay. Well, let's look at another one of the studies that you showed us. This one is the one from Denmark by Madsen. This is Petitioner's Reference 239.

MR. MATANOSKI: Just for housekeeping, I know that when we referred to the Schechter Grether, we had referred to it, it's apparently been submitted by both. And I think it's Respondent's 439.

BY MR. WILLIAMS:

Q Now, this is another one of the studies that you cited as support for the proposition that there's strong evidence that thimerosal had no effect on the rate of autism in Denmark. That's right, isn't it? This is the one you cited?

A I don't know if I used the words "strong evidence," but yes, it's another piece of the evidence which is consistent and robust across studies.

Q Let me find -- what is your slide number for this? No. 12?

A Twelve.

Q Okay. And Scott, in the paper that's on page 2, is figure 1 I think, blow that up.

Now, the rates, the incidence we're talking about here in this Madsen paper are not per 1,000; these numbers are per 10,000 on the left-hand column, right? The incidence per 10,000?

A Yes.

Q And from 1970 until about 1990, they have the incidence rate around, what, .2 or .3 per 10,000? Now, don't you think that in 1985 and '90 the true rate of autism in Denmark was about 60 to 70 per 10,000?

A It was probably much higher than that, yes.

Q Much higher than that, okay. And that would be on this chart, if we had this line reflecting the true rate, say in 1985, we'd have to be up around the ceiling. Because this is a scale of one, two, three, four, five, and we're talking 60 or 70, right?

A Yes.

Q Do you think that these are reliable numbers on which to rely for evidence of a change in trend in incidence? These numbers back in 1985 and 1990?

A It depends to study what.

Q In order to look for changes in the trend.

A Yes. Well, again, it's not -- it's the same question as before. Your trend, the prevalence or the number of cases which are captured or identified over a period of time can be an underestimate of the true phenomenon. But still, within that, these constraints, you can look at what risk factors are associated with the disease.

So for instance, take gender. In the first period of 1970 to 1990, you would still find that there are three males for one female affected. So that would be still a good estimate of the association between gender and autism, despite the fact that the number of cases identified is an underreflection.

Q So even though it's an underestimate by about 99 percent, it's still reliable data on which to base your conclusion?

A Well, you can certainly base conclusions, for instance, in looking at, if you look at, as I said this morning, the fact that the beginning of the period, children aged two to nine were exposed to 200 micrograms of ethyl mercury in Danish vaccines. That tells you something about the fact that there was no clear increase in the incidence of autism due to these high levels of thimerosal.

And when it's decreased 125 in around the

mid-seventies, there is no evidence that the rates are decreasing, neither. And if you look at that in a narrow way, when it's decreasing, or the exposure is decreasing or is removed, as is the case in that particular study, you expect to find a change. Under a background of, underlying noise, as you said.

Q Let's look at the right-hand side of the scale, after the new diagnostic criteria came into place in '92 or '93 or '94, and after they added in the inpatient data, I mean the outpatient data, as well as the inpatient data.

What is the final estimated incidence rate for 1999 in this study?

A In let's say 2000, for instance?

Q Yes, or 2000. It looks like the highest one I see is about four, maybe to give you the benefit of the doubt, five per 10,000, right?

A Uh-huh.

Q That's an underestimate by your numbers of at least a factor of 11. And you're saying that that's still, despite the fact that they only have got five per 10,000 in 1990, that that's an accurate enough number on which to say thimerosal had no effect.

A I think you need to look at the

classification that they used, which is ICD-10, in which they used in that particular study the code 84.0 and 84.1. Which in ICD-10 mean autism and atypical autism. In ICD-10, that does not account for PPDNOS.

Q Okay. So it may be only an underestimate by a factor of four or five.

A I don't know.

Q Well, what do you think the -- I thought you said that you thought the present prevalence of autism itself was around 20 or 25 per 10,000?

A In recent surveys, yes.

Q And in the year 2000 you said in Denmark, it's probably even higher than that. I thought I heard you say in Denmark it was higher --

A No.

Q -- than 66 per 10,000.

A No, I didn't say that. I don't think so.

Q You think it's the same?

A For all ASDs combined?

Q Yes. Well, let's confine it to autistic disorder. What do you think the prevalence was in Denmark in 2000 of the narrower category of autistic disorder?

A Oh, I don't know. I can make educated guesses.

Q Well, what do you think, what is your best estimate?

A In 2000? I don't know, probably the prevalence would have been 10, 15, per 10,000, in their recording system, probably that kind of findings. And you have to also look at age. It has to be age-specific.

So I think in the Denmark data, if you look at the Atladottir paper, there are actually, in a given birth cohort, when the birth cohort ages even beyond age 10, they keep accruing new cases in the same birth cohorts. And it's unclear why, but it seems that there are late diagnoses or late reporting in the same birth cohorts.

So when you look at age 18, there are figures actually getting closer to what you would expect. I don't have an explanation for that. And what I can also say, that in the recent studies in Denmark show rates for ASDs which are like 62 in the Atladottir paper, and there is a new paper coming out which is showing a rate of PDD which is 80 per 10,000.

Q Eighty? Eight-zero?

A Eighty, eight-zero, yes. At age 18 or 15. So they are -- and of course, this is under a situation when there is no TCV vaccines.

Q Right. Now, we could do the same exercise with the other negative studies, but I just want to look at your Montreal study for a moment.

This is Petitioner's Master Reference List 40, four-zero. And you showed, I think, a figure out of this paper in your slide. What slide number was it? Maybe you didn't show the figure.

A No, I didn't show this.

Q Oh, yes, you didn't show the figure. Well, let me show the figure, then. It's figure 2 on page 6 of this paper. If you could blow that up, Scott, the whole figure 2. That's good.

Now, you've got prevalence rate per 10,000 on the left-hand column, right? I mean, the left-hand scale is prevalence per 10,000.

A Yes.

Q And then you have grade years and years of birth at the bottom, right?

A Yes.

Q And you have one prevalence rate, the lowest one in the birth year '88, you have as low as 27.5.

Now, you're sort of, you know, the gold standard for assessing prevalence of autism. But how did you get such a low number, if the real rate is about 60 or 70 per 10,000?

A These are children who were born in 1988. It's very likely that a lot of them have been not diagnosed, or maybe in different educational systems, I don't know. But there is suddenly an underascertainment in the earlier birth cohorts. And what happened in Montreal is that expertise in the diagnosis of autism awareness and services, both in the educational system and in terms of community providers for behavior interventions have only developed in the last six or eight years.

So it's really recent. And then, of course, more children are diagnosed in the younger age groups. But it's clear that in the oldest age groups, they, there was clear underascertained.

Q So if we wanted to have a reliable number for the prevalence rate in grade 10 or year '88, we'd have to change that from 25 to 65, wouldn't we?

A Yes, I suppose. It's one way to present it.

Q And then the highest rate you find is almost, is 107.8 per 10,000.

A Uh-huh.

Q That's the highest figure I've seen in any study so far. Are there higher ones than that published?

A Yes.

Q How high have we gotten so far?

A It was one British study by Byrd, et al, which has a rate of 1.16 percent. So 116 per 10,000.

Q For the full ASD spectrum.

A Yes.

Q Do you know what the breakdown was for the four categories in that study?

A Not off the top of my head. I think the rate for autistic disorder was 38, but I would have to check. I don't recall.

Q Now, there's another figure above this one I want to show briefly, figure 1 just immediately above this on the same page. This seems to be presenting the same data, because the point estimates are the same numbers as in figure 2. But now you've given a range for each point estimate. Is that some kind of confidence interval?

A They are confidence intervals.

Q And if the point estimate of, say, the 1998 year is included within the confidence interval for the 1997 year, don't you say that statistically those are really the same number? They're not statistically different?

A If you compare two data points only, yes.

Q Now, another question about this study.

You're comparing two populations of children here, as I understand it. The children in which you have got estimates of their thimerosal exposure came from one population, and the children in which you've got estimates of their autism rate came from a completely different population. Right?

A Yes. Well, what are you talking about exactly? Estimates of what?

Q I was asking for your estimates of autism, of thimerosal dose. Your major thimerosal dose came from one population.

A No.

Q No?

A No. No. On the screen you have estimates of MMR coverage in that study. That came from a series of surveys done in Quebec City, which was the only reliable series of surveys of MMR coverage which was consistent over time, the methods used that could give us a sense of how well vaccinated were Quebec children with MMR. So that is shown here, on the with a slight decline over time in MMR uptake, based on this Quebec series.

And you were right that this was done in Quebec City, because it was the only public health information that we had that could be used. And by

the way, it shows a downward trend, and last year there was an outbreak of measles in Montreal, which probably indicates that this trend was actually a valid one.

Now, for what we are talking about today, we are talking about thimerosal, this is not based on estimates or surveys. It's based on the official immunization schedule, which is, you know, enforced -- not enforced. It's decided by public health authorities and pediatricians, it's a committee, so it's all well organized. Vaccinations are given very widely in Quebec.

But the estimates of the amount of thimerosal was not based on a survey. It was based on the regular immunization schedule of children in Quebec.

Q Now, has anyone ever asked you to produce your raw data for this study, for their examination?

A For --

Q Some outside investigator? Ask you for your data?

A I think someone has asked for that, yes.

Q And you refused to produce it?

A Yes, because it was kind of a bizarre request by a bizarre person.

Q Now, let's turn to your criticisms of the Young, Geier study for a moment. And we'll use Petitioner's Reference List 665. Let me pull it up here. Do you have a copy of that with you? I can get you one.

A No, I have it.

Q Here's a copy.

A I prefer my copy.

Q Oh, your copy has notes on it.

A I might have notes on it.

(Pause.)

Q Now, the first thing I wanted to call your attention to is in the materials and methods section. But first let me ask you, the journal in which this was published, which you didn't put on your slide, this is the official journal of the World Federation of Neurologists associated with the World Health Organization. Did you know that?

A No, I didn't know.

Q You didn't check that out?

A No.

Q And it was fully peer-reviewed? You do at least admit that, don't you?

A Yes.

Q And in the materials and methods section, if

we highlight the first paragraph, Scott. Yes, blow it up. It says that the study protocol employed was approved by the U.S. Centers for Disease Control and Prevention.

Did you know that the protocol had been submitted to them for their review and comments?

A No.

Q You didn't?

A No.

Q Then after the CDC approved the protocol, this protocol for the study had to be submitted to the Institutional Review Board of Kaiser Northwest -- that's in Portland -- and the IRB of Kaiser Northern California. You did know that, didn't you?

A Well, I read what is in the paper, but I don't have access to these protocols, written protocols, and the extent to which it was approved by the CDC. I don't know what it means, so I would reserve any opinion on that.

Q And, well, let me just ask you. Do you know that one of the restrictions placed on access to this data by the CDC was that the investigators were not allowed to compare to total vaccines for any one child?

In other words, they could look at a child's

DTP records, or they could look at a child's Hib records, but they couldn't combine those files in any way to do statistics on a single child's exposure. Did you know that?

A No, I didn't know that.

Q Did you also know that they were denied any access to data after the year 2000?

MR. MATANOSKI: I would just like to find out what the basis for that last statement was. Was it in the -- I just want to request clarification about the basis for the facts of the last question. Is it in the study?

MR. WILLIAMS: I think you'll get a chance to deal with this later. I mean, if it becomes a contested issue, we can deal with it.

MR. MATANOSKI: Well, this study, in terms of the IRB approval, et cetera, has already been a matter of litigation here. If the Court recalls, there were some motions that were made, and some indication during that that there was actually violations of the protocol, violations of the approved protocol by the IRB. That was part of the request that was before this Court before.

MR. WILLIAMS: With all due respect, I think this is for redirect or for argument, not for --

MR. MATANOSKI: Well, I can't redirect this witness on something that he wouldn't have any knowledge of. And that's why I was trying to find out what the factual basis was for the last question, if it's not in this study as reported.

MR. WILLIAMS: We could provide it. We can get a letter from one of the investigators, as you have gotten letters from your --

SPECIAL MASTER VOWELL: Again, Mr. Williams, we've been through this before. Please address your remarks to the Bench, not to one another.

Let's try that again.

MR. WILLIAMS: I believe that there is a firm evidentiary basis for the questions I'm asking. And we can provide that with a letter from Dr. Young if need be.

SPECIAL MASTER VOWELL: Understand that his answers are not going to be informative to the Court without, whether he says yes or no, if we don't know what the basis. You're asking him if he knows something. If it's true, he can say no, and if it's not true he can say no, he didn't know. He doesn't tell us whether it's true or not.

So what I'm telling you is if you want us to consider the limitations, if any, placed on these

investigators, then you're going to need to provide that to us.

MR. WILLIAMS: We'll be glad to. But I did want to know whether he knew about these restrictions or not, since he was critiquing the paper.

SPECIAL MASTER VOWELL: And you can ask.

MR. WILLIAMS: Okay.

BY MR. WILLIAMS:

Q Second question. Did you know that the investigators were denied access to any data after the year 2000 in the Vaccine Safety Datalink?

A No.

Q And the imputation methods that they used were required, were they not? If they didn't have access to the further later diagnoses of these birth cohorts, what other method could they use besides imputation of estimates of diagnoses?

A They had a problem with the data. I think they could not just do the study. And instead of adding numbers which are completely invented, there are other techniques that could have been used. Or this would simply, do not perform this type of analysis. It's dishonest to impute like 45 new cases which are just invented to top up the prevalence in a way which is supportive of their hypothesis. It's

clear that these investigators have a clear track record to do with the data what supports their hypothesis. And I've seen that in their previous papers. And I think that is what they've done here.

I think it's, you know, it's unacceptable. And the fact that this paper is published in this journal doesn't surprise me, sadly, because the peer-review process is not entirely perfect, as we all know. And it's, of course, you would imagine that in this editorial board, the expertise for dealing with the epidemiological analysis of this type of data is probably lacking. And it's unfortunate that it has been published.

But I can tell you it would not have passed any stage of reviewing in autism journals.

Q Now, you said they're dishonest. The imputation is not hidden in this paper.

A No, I know.

Q So what is dishonest about the imputation? If it's revealed in the methods, and can be tested by other investigators.

A No, because it's impossible to check their assumptions about age of diagnosis. We don't know how they came up with these figures of 45 and 80. They explain it, but not fully, so you cannot actually

check the accuracy of their adjustment methods.

And what is also dishonest is that the use of the 1990 birth cohort, which is based on 0.6 percent of their sample, this is also something which is maybe not dishonest, I don't know, because it's a judgment which I make which I shouldn't probably make. But it's actually incompetent.

Q Do you know that the datasets that they used to analyze this, as well as their protocol, are fully available to the Respondent here? And this can be duplicated, checked very easily by Respondent's experts. Did you know that?

A No.

Q Now, you referred to papers by the Geiers in prior epidemiological studies they had published that had been reviewed by the IOM committee in 2004.

A Correct.

Q Every one of those papers was using a different database, wasn't it? It was using the VAERS database, which is just a spontaneous reporting database.

A Which is inappropriate to test vaccine adverse events.

Q And no one here has been citing that or relying on any of those studies. This in the Vaccine

Safety Datalink database, the same one Verstraeten used. You agree that's a good database, don't you?

A Well, I don't know it intimately, but yes, it's a database which is probably informative to look at adverse effects in relation to vaccines and other questions, if you use it properly. Which means that you need to use the full opportunity that a cohort gives you when you can.

If they were not able to do that for legal reasons, I don't know. But it doesn't salvage their study.

Q Let's turn to the topic of regressive autism. I want to go to your report on paragraph 37.

(Pause.)

MR. WILLIAMS: If you could put -- do you need another page number, Scott?

BY MR. WILLIAMS:

Q Now, this is where you discuss the Richler paper. And I understood you to be writing paragraph 37 with the intent to push this idea, that true regressive autism where there is no evidence of any abnormality before the symptoms of autism develop, no evidence of abnormal development until autism appears, that that type of regression was very small compared to all regressive autism. Isn't that what you're

trying to say here in paragraph 37?

A Not exactly. I was probably trying to -- this is kind of showing historical change in the field about how we viewed regression. So initially I think Dr. Lord stated that this morning, that regression of loss of skills, which was a recognized phenomenon, was often equated with the fact that development was normal before. So there was no differentiation of these two things: the loss of skills and what happened before.

So there was an assumption that the development was normal before the loss. And then this paragraph states that in fact, increasingly, as we have done studies of regression, this assumption has proven to be challenged more and more, up to a study like Richler et al. on a large sample size, which indicates that in fact, when you look carefully at these children who have regressive autism, in 72 percent of them you can actually document abnormalities.

And the fact that there are 28 percent in which you don't document this abnormality is not a demonstration that 28 percent of these children have normal development. It just simply reflects probably the fact that in this particular study, with the tools

that we have which are based on retrospective parental report, there were a group where there was no evidence based on the questions which were used.

But the idea is that as we go along, and if we can do, for instance, prospective studies of large numbers of children that will ultimately lose skills, it's pretty clear that an increasing proportion of those who will lose skills would be documented to have subtle abnormalities before their loss. And this proportion could go up to 100 percent, I don't know. But that's the trend.

Q In your own study of the MMR vaccine, you used the definition you called definite regression. You used, you had probable regression and definite regression. Let's put that up. You had a slide about this.

A Yes, yes.

(Pause.)

Q And your slide 23 I believe is out of the paper that we're about to put on the screen. No, it's not that one; it's the Fombonne and Chakrabarti. You brought it out for me.

(Discussion held off the record.)

Q You cited this paper in your slide. Do you have a copy of that paper with you? No? We have a

copy here somewhere.

Well, while we're looking for it, let me tell you what I recall your definition was. As I recall, your definition in your materials and methods section of this paper was that definite regression was defined as a measurable loss of at least one skill or outcome, in one of the three domains of autism. In other words, they either lost language, or they lost social skills, or they lost the play factor.

You didn't require that they have lost two or three, just one. Do you remember that?

A I don't. I have to look at the paper. But the differentiation between definite and possible is based on the ADI. So it's attached to a particular operational definition, which are included in the ADI. So maybe it's summarized well in the paper; maybe you will have to have an ADI interview.

Q Can you find it over there?

A I have it.

SPECIAL MASTER VOWELL: Which one do we think it is?

MR. WILLIAMS: Well, it's the one he cites on his slide 23.

MR. MATANOSKI: RML-147.

SPECIAL MASTER VOWELL: Okay, that's the

Pediatric article.

MR. MATANOSKI: Yes, ma'am.

SPECIAL MASTER VOWELL: The "No Evidence For A New Variant of Measles-Mumps-Rubella Induced Autism"?

MR. MATANOSKI: That's correct, ma'am.

SPECIAL MASTER VOWELL: Okay. So we're looking at RML-147. Yes, there we go.

MR. WILLIAMS: If you could put the materials and methods sections up, where he defines regressive autism. I think it's on page 3 or 4. The next page, Scott, I think. Yes, there it is. Definition and assessment of regression.

SPECIAL MASTER HASTINGS: Which page was that?

MR. WILLIAMS: I can't tell from this.

MR. POWERS: Page 4 of the exhibit.

MR. WILLIAMS: Page 4 of the exhibit. And it's the section of the paper entitled in bold, "Definition and Assessment of Regression."

BY MR. WILLIAMS:

Q And I know you're reading it, Doctor. Why don't you just tell us what definition you used for definite regression?

A It's the definition which was in the ADI,

the diagnostic interview that we all use, which was used at the time. There have been a few changes since early 2000 in the overall section on regression.

At the time, to have definite regression you needed to have demonstration of, for language for instance, you needed to have at least to demonstrate that the child had used, for at least three months, at least five words other than mama and dada, which were used spontaneously on a daily fashion to communicate. Okay? So this, when you think of it, it was all the emphasis I put is actually quite a stringent criterion. The child needs to have at least five words used daily to communicate for at least three months. So it's a very stringent criterion.

Then when there is a loss of that, the language had to be lost for at least three months. So that was the way it was operationalized. And it was at the time where I think people were trying to get a common way to evaluate language loss in the course of development of children with autism, whereas before that there was no common rule or common tool. So that was quite a stringent way to define it.

And based on that, the rates that we have are somewhat on the low end, 15 percent in the recent sample, 18 percent in the previous sample. Not

statistically different, but it was because of the use of this rather stringent definition.

Q I must be misreading slide 23. Because it looks to me like the definite regression is only about eight percent, on slide 23.

A Oh. I was talking about the combined rates of definite and possible regression.

Q Okay. Now, Scott, let's go down to the next paragraph immediately below this, where I think it talks about other measures of regression besides language.

You were saying for language skills, it's required that they have at least five different words, et cetera. And you said if this criterion is met, then the loss is defined as the absence of use of words.

Then you say the loss of a specified skill that does not meet these stringent criteria, nevertheless can be coded as probable if there is sufficient evidence of regression.

And now you're talking about more than language, aren't you?

A No, it could be like a child having four words for two months, and then he lost them. That would be probable, but not meeting full criteria for

the definition.

Q And then, let's see the rest of this section, Scott, at least on that page.

You talk about regression being assessed in the Stafford sample by identifying any probable or definite loss of skills in one of the seven domains.

You had a very precise definition of definite regression in this paper, didn't you?

A Yes. It was following again what was in the ADI. So we were covering regression by domains, as it is part of the interview on regression in the ADI.

Q And then at the top of the next page, still in this section.

A Okay.

Q You say that for the MFS sample, what does MFS mean?

A Probably the Maudsley Family Study.

Q Okay. A slightly different version of the ADI was used. And again, what does ADI refer to?

A Autism Diagnostic Interview.

Q And regression was defined using three items of the original ADI version that assessed probable and definite levels of regression and loss of skills in the first five years of life, and in three domains: language, social actions, and play imagination.

So did you use actually two different definitions of definite regression in this study?

A No. It's more that in the more recent version of the ADI there had been an exploding of some items which were, there were like, for instance, three or four questions. But in the more recent versions, you had probably seven or eight questions covering different skills within the same domain.

So it was, we could actually make comparisons across the two instruments, because I excluded, I looked at up to age five, I think, because otherwise they were inclusion of lifetime loss of skills that would have confounded the comparison. So it was quite comparable.

Q Now, has this official definition of regression been modified since you wrote this paper?

A I don't see it as an official definition. It's like --

Q Well, you were getting it from some instrument, weren't you?

A Yes. Yes, okay, yes. So the ADI has been devised in the middle eighties, and it has changed, has evolved as an instrument. So the regression items as part of these interviews have also evolved, and there have been different iterations of the interview.

And in the most recent version, which is in 2002, it's yet to be different than it was before.

But in most cases, when we make modifications, and in this particular instance Cathy Lord and others make them, they try as much as possible when they refine an instrument to ensure that there will be comparability if you need to compare with previous versions, that it's possible.

So for instance, if you refine a question, if you have three items in version 1, and you take the three items and then you ask two questions for the three domains, you have six items in version 2. But you can combine your answers to make it comparable to the version 1 if you need for that analytical purposes. So we try to do that as much as possible. Sometimes it's not possible.

SPECIAL MASTER VOWELL: Dr. Fombonne, I'm confused. Does the ADI contain a definition of regressive autism?

THE WITNESS: No.

SPECIAL MASTER VOWELL: So this is your definition, using the ADI.

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Okay. Now I'm not confused.

BY MR. WILLIAMS:

Q Go ahead.

A There is no definition of regressive autism. There are questions asked to parents about loss of skills in the course of the development. And these questions are operationalized in such a fashion that we establish a baseline; there was a skill, it was lost for a certain duration of time. And then, when this is met, that's what we call this child had a regression. Then we call him or her, loosely, it's a regressive autism child. But it's just that we had a loss of skills in the course of his development, as reported by the parents in the course of this interview.

SPECIAL MASTER VOWELL: Let me ask it this way, then. Is the ADI used to diagnose autism?

THE WITNESS: Yes.

SPECIAL MASTER VOWELL: Does that diagnosis contain a separate subcategory for regressive autism in the ADI?

THE WITNESS: No.

SPECIAL MASTER VOWELL: Okay. I thought I understood you; I do. Thank you.

THE WITNESS: Just maybe to expand on that the ADI must have versions, had 120 questions in some

versions. But those critical items which are important for the diagnostic algorithm are just a subset. So maybe 25 items would be critical for scoring the presence or absence of PDD in a child.

Many questions, like the regression items, do not play any role in diagnosing a PDD or not. They are just like extra clinical characteristics that we collect, as we would collect data on self-injury, seizures, items on that. So they are not diagnostically important.

BY MR. WILLIAMS:

Q What group approves changes in the ADI? Is it some kind of consensus when they modify it?

A Yes, consensus or lack of consensus at times. We try to base decisions about changes on empirical data. So I have, myself, contributed to studies with Cathy Lord and Michael Rutter about looking at algorithm of the ADI and how it relates to other kinds of clinical characteristics, to improve the algorithms.

So I've published on the ADI in 1992, in a special issue, which was preparing for DSM-IV, for instance. So we try to derive our decisions about changes based on empirical data that we have, and that we sometimes share and put in common. And then often

there are discussions about different investigators, about some that are very interested in adding questions of that kind, others that are not interested. It's going to increase the length of the interview, so there are toing and froing, and at the end a compromise.

Q And one of the reasons that the group of experts that put together the ADI have added these agreed-upon regression questions is to try to standardize studies that want to look at regression as one factor in assessing autism, right?

A Yes. It's not assessing -- yes. In evaluating the developmental course. Not trying to derive diagnostic subtypes. It was never used in that way.

Q Let's look at slide 24 for a moment, of your slides. This is another regressive autism study that uses the term, the terms "probable" and "definite regression." Were they also using the ADI to make this assessment?

A From my recollection, no, but I would have to check back on the paper.

Q We'd have to look at the paper and see what the methods were.

A I think what's important is that they

probably, whatever tool they used to define probable and definite regression, that they did that consistently over the years of the study. That's what matters.

Q Right. And assuming they applied the definition of regression consistently, we see that it fluctuates from a low of about, what, seven per 10,000 in 1988 to a high of as much as almost 40 per 10,000 in the year 1994, correct?

A Uh-huh. That's correct. I'm not sure, you read that on the right vertical axis?

Q You used the right axis, which is the incidence per 10,000.

A And you said?

Q If we go to your slide 27, which showed the rates of, or the percents of regression in the CDC survey, you already pointed out that there is almost a threefold difference between the lowest regressive rate in Colorado, and the highest one in Utah.

Do you know if those states were using the same definition of regression?

A It's not threefold, it's like 2.4, 2.5.

Q Okay, two-and-a-half-fold.

A Okay. Yes, there was a common definition used by the CDC when they were abstracting recalls of

all the data collected about each child. So they used a common definition. I don't have it here. But I know they had high inter-ratio reliability if I retained that. So I think their reliability figure on that was over 97 percent.

In other words, two abstractors would agree almost all of the time with respect to the presence of absence of regression in a particular child, using their scheme.

Q We're almost done. I wanted to show you one more study. This is the study you cited on regression, by Dr. Lainhart and others. This is Petitioners' Master Reference 91.

MR. WILLIAMS: Do we have a copy I can give to the Doctor? Okay, thank you.

THE WITNESS: Thank you.

MR. WILLIAMS: And if you'd show the title and the date there, Scott, just so we can get that in the record.

BY MR. WILLIAMS:

Q This is the paper you cited in your report, right?

A Yes.

Q Yes. Published in 2002. And in the abstract of this paper, the last sentence -- let me

blow that up and highlight it -- actually, the last couple of sentences. They're talking about, as you made the point, that the measure of genetic liability is increased essentially equally in families with both forms of autism when compared with controls. That was the point you made on direct.

A Uh-huh.

Q But doesn't the paper go on to say that environmental events are therefore unlikely to be the sole cause of regressive autism in our sample? Environmental events, however, may act in an additive or second-hit fashion in individuals with a genetic vulnerability to autism.

Do you agree with that?

A I certainly have no disagreements with that statement. The importance of that study and studies which were done on regression at that time is that it showed that in children who regressed, there seems to be the same familial loading of autism-wide autism phenotypes. And it was important to document, because there was at the time, following Wakefield's claims, in 1998 he claimed that he had discovered a new phenotype, which was regressive autism, which was entirely environmentally induced. That's how he started.

So that study holds out regression as being entirely environmentally triggered.

Now, you can still say that maybe the genetic susceptibility is there, but then there is a double-hit mechanism, that's fine.

Q And then, just to go to the very conclusion of this paper, on page 6, Scott, right above the acknowledgement section. Just pull that top paragraph up.

These authors say that even if genetic risk factors are most important in autism, the wide variations in autism and in the autism and broader autism phenotypes and associated features still warrant a thorough search for environmental factors that may affect severity of the disorder.

Do you agree with that? That there is, it is warranted to do a search for environmental factors that could be bringing on autism in some of these children?

A I do not disagree with that statement. And if I have been involved in looking at MMR initially, it was because I was concerned about contributions of environmental factors in autism. And I've been doing that in other conditions, as well.

So I think environmental factors are a

candidate of risk mechanisms for autism, probably in the context of genetic susceptibility. So I disagree with the reasoning in the first part of the sentence, because we have, as was stated by someone else -- for instance, if you have monozygotic pairs of twins, we are concordant for autism. So you have, they are both having the same set of genes, 100 percent of genes. And both of them have autism. You still have a huge variability in the phenotype. One can be high IQ, and the other one can be very retarded. So it has been demonstrated in the British twin studies in particular.

So it seems that there is an aspect of the severity of the phenotype which is not entirely determined by genes. It doesn't mean necessarily that it is determined by an environmental factor. It could be just random effects about neuronal development which are not particularly controlled by environmental mechanisms. Or it could be genetic effects which are not inherited.

So it's a kind of jumping from, to environmental because of the wide variability of the phenotype, is a bit of a --

Q Okay. Now, this is going to take you back to almost your first slide, where you were describing

the types of epidemiological studies that are available to researchers. You talked about the cohort study. And the case control study is best used when you have a very rare condition.

Because, for example, if we take autism rate as one in 150 as an estimate, and we assume that definite regression is only 10 or 15 percent of that, then you would expect to find the prevalence of definite regression only to be one in 1500, one in 1200, something like that. Is my arithmetic about right?

A Yes, about.

Q So if you were going to try to do a cohort study to look at environmental causes of regressive autism, you would have to have hundreds of thousands of children to see an effect, wouldn't you?

A Probably, yes. You're probably right.

Q Whereas if you did a case control study, and you could identify 1,000 children who met an agreed-upon definition of regression, and then get two or three thousand controls, you could do a pretty powerful study looking for environmental factors with just three or four thousand children, couldn't you?

A Yes.

Q Don't you think such studies ought to be

done?

A Well, I mean, you don't launch studies just because you can just do it. You have to have an hypothesis, and you need to be looking for something.

I can just add to that that there are ongoing case control studies based on population series of cases which are looking precisely at environmental risk factors, in what we call epidemiology fishing expeditions, where we don't have much of a strong hypothesis about what the mechanisms might be.

The CHARGE study, for instance, where the Hansen's paper is coming from, is part of a case control study based on children recruited in the population, which is looking at a broad array of environmental factors looking at prenatal factors, factors in the household, heavy metals, all sort of things.

So they are looking at a wide range of things, because there is no good lead about where to look for initially. But the design is one of a case control study for the reasons that you mentioned.

Q And you would agree that mercury, being one of the heavy metals, should be on the list of environmental factors looked at in such a case control

study, don't you? Mercury exposure?

A I don't have much evidence so far that mercury is a risk factor for autism. So I'm not sure. I wouldn't put my eggs here.

Q Sorry. Did you mean all the heavy metals other than mercury?

A No, I didn't say I would do it. I think they are doing it. I don't think this is where I would be looking at.

Q You don't think it's a good idea for them to be doing it.

A I don't think, if you asked about mercury, again considering the epidemiology that we have in terms of both the ethyl mercury vaccines and the methyl mercury data relating to the epidemiology of autism, I think there is no convincing starting point here.

Q Have you looked at the infant monkey studies, the adult monkey studies that we have been talking about throughout this trial?

A Yes, briefly. But I'm not a monkey person.

MR. WILLIAMS: Thank you.

SPECIAL MASTER VOWELL: Redirect?

MR. MATANOSKI: Ma'am, as I understand, there's still more cross to come?

SPECIAL MASTER VOWELL: Oh, yes. I'm sorry, that's correct. Rather than redirect. Yes, rather than starting redirect now, let's go ahead and do the individual cases.

MR. POWERS: Special Master, if I could propose, given the time and knowing that I have some cross, there might be more redirect and some further questions, a short break now as the afternoon break.

Mine will not be so long as Mr. Williams's, but it might be a good time for a break nonetheless.

SPECIAL MASTER VOWELL: How about if we return in, say at 4:00?

MR. POWERS: That will work for Petitioners. Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER VOWELL: We're back on the record. Dr. Fombonne is still on the witness stand.

Mr. Powers, you may do your portion of cross.

MR. POWERS: Thank you, Special Masters.

FURTHER CROSS-EXAMINATION

BY MR. POWERS:

Q Good afternoon, Dr. Fombonne.

A Good afternoon.

Q My name is Tom Powers, and along with Mike

Williams, I represent the Mead and King families, as well as the Petitioners' Steering Committee.

I want to focus my questions specifically on the testimony that you gave regarding the two individual cases here, that of Jordan King and William Mead. And just as you began, I'll talk about Jordan's case first.

But before getting into that, if I recall, you were here during Dr. Lord's, Professor Lord's testimony?

A Yes.

Q And at one point Professor Lord testified about the importance of parental accounts, and the thorough histories that a parent would give. Do you recall that testimony?

A Yes.

Q Would you agree with Professor Lord that detailed parental accounts, often prompted by questions, provide the most reliable historical information upon which to base assessments of regression, and the onset of autistic symptoms?

A No. I agree if you are asking that retrospectively, that's the best source. Now, there would be other ways to study a regression or loss of skills in the developmental course of autism, by

conducting very tightly controlled prospective studies of high-risk samples.

Q What we're talking about here in these two cases were obviously retrospective, correct?

A Okay. So retrospectively, yes, I would think that asking parents would be the best source available, although it doesn't mean free of bias.

Q And when you say "free of bias," what are you referring to?

A All sorts of evidence in psychiatry, in psychiatry studies, show that when you interview people about their past experiences, that you can have a lot of recall biases occurring.

So for instance, in psychiatry dating the onset of symptoms has been a problem in research for decades. And that's why we use sometimes lifetime estimates of -- I don't want to get into details. But it's known in psychiatric epidemiology that when you try to interview people and reconstitute their life trajectories in terms of symptoms or episodes of disorders, it's very hard to actually get to an accurate picture, when you compare to contemporaneous records or other information.

So it's not an area which is easy. But there have been some techniques of interviewing which

have been devised to improve the accuracy of recall, but it's not perfect.

Q Yes. Certainly recognizing it's not perfect, but the parental history combined with the opportunity to examine contemporaneous medical records, given that we can't travel back in time and relive the experience, is the most reliable way that we can go about reconstructing these histories, is that correct?

A I would agree.

Q Now, let's talk about Jordan King in particular. In your expert report on page 61 -- and I should ask you, do you have that report in front of you?

A Yes.

Q On page 61 at the very top of that page, let's see if we can pull it up here in a second. That very first paragraph that begins on the preceding page, but that first paragraph up at the top, which would be paragraph 137, continued. Let's go ahead and highlight.

Now, if you recall, Dr. Fombonne, this is a developmental services interview that was conducted when Jordan was 26 months old, is that correct?

A Correct.

Q And what you're referring to here is Mylinda King's -- that's Jordan's mother -- giving an account of Jordan's development. So she's giving this account at a point when Jordan is 26 months old, correct?

A Correct.

Q And she describes retrospectively that he used single words at about one year of age, and then stopped.

Now, when she testified, were you here for that? Or did you listen to it?

A I listened to the audio recording.

Q And did you hear her on redirect, when she came up and clarified a note in the medical record about when Jordan stopped talking relative to his having words at one year? Do you recall that discussion?

A Not specifically.

Q Well, Mrs. King testified that there had been a note in the medical record that Dr. Rust identified, saying that Jordan spoke at one year and then stopped. Dr. Rust was implying that he stopped, that he, Jordan, stopped speaking at one year. Mrs. King clarified that he stopped speaking well after one year, but before age two. Do you remember that?

A No, I don't recall that, but that's what I

would have understood.

Q Okay. So at age 26 months, Mrs. King, as you understand it, is not saying that Jordan lost his words at one year of age, but he had words at one year of age and lost them later. Is that your understanding?

A That's what I understood.

Q She also described him having multiple words: juice, shoe, up and down, I believe, that he could say cat and dog. Do you recall that he had at least four or five words by the age of 12 months?

A Yes, I recall mama, hot, daddy, shoes bubbles, mailbox, tiki. So that's five or six words, yes.

Q And you recall her testimony that he started using those words a little bit before one year of age, and continued using those words past one year of age, correct?

A Yes.

Q And that he used those words appropriately, that is, in context. He wasn't calling his breakfast cereal a mailbox, he was talking about the mailbox when he said mailbox, correct?

A Yes.

Q So you have described, in discussing

regression, this criteria of having at least five words, and using them regularly for at least three months. So from the evidence that's come in in Jordan King's case, it certainly sounds as if he had at least these five words, five or six words, and perhaps more words, and used them for a period of several months. Isn't that correct?

A No. I mean, that's an inference that you made. I want to be the devil's advocate here.

He has, based on Mrs. King's testimony, and records let's say five, six, seven words at age 12 months, fine. Now, you need to assess the quality of the use of the words.

In the definition that we use, we need to be sure that these words are used spontaneously. And that's very, very -- that's a qualifier that is extremely important. Because there are many, many parents and autistic children who start to develop words, but they don't use them spontaneously. So they just copy or they echo their parents.

So the parents say horse, this is a horse; and then the child repeats horse. This is not counted as spontaneous communication. So you need to assess the quality and the functionality of these words. Are they used spontaneously?

And in his case, if we are to follow the ADI definition that we discussed previously, we would need to ascertain that he was using these five or six words daily for at least three months, before having lost them for another period of three months, which we cannot do, I think, based on the existing record.

Q And there's certainly nothing in the record that indicates that the words he was using were nonspontaneous. There is no indication that this was echolalia. In fact, Mrs. King testified that he used words spontaneously, and in context. That was her testimony.

A Yes. And he was pointing as well. So I'm not disputing that. But I think to apply the full definition that we use, we would need more data that we do not have.

But I agree with you, based on my own opinion, that it's the testimony and the parental recall that he had words; that he lost them at a later point.

Q And not only did he have words, I mean words, I think Dr. Lord testified about this also, word count is but one manifestation of language skills or communication skills, correct?

A Yes.

Q And she actually testified that word count may not be the most important, particularly for toddlers, correct?

A Uh-huh.

Q I know that you're saying yes --

A Yes.

Q -- but the court reporter is going to need to know that.

A Yes.

Q Now, the testimony that we heard from Mylinda King was that Jordan used all sorts of other ways to communicate well into his second year of life: pointing, gesturing, grabbing his shoes and bringing them when he wanted to go outside. You remember all of that testimony.

A Yes.

Q And all of those are communication skills, particularly for a toddler. They may not be words, but those are skills in the communication or language domain that a toddler would expect to be demonstrating by that age, correct?

A Yes. But again, I'm sorry, I don't want to be -- what matters is the quality of these gestures. Many, many -- let's take the example of pointing, for instance.

Many children with autism do point. They point for expressing needs. So that's a kind of pointing that we call protodeclarative. So if they want biscuits, they will point to the biscuits like this.

But there is a type of pointing that they don't do, which is pointing at a distance. Because if I am talking to Mr. Powers, look there; I'm pointing at this object. I look at it, I point with my finger, I speak, and I check back that you are following my point. This is a different type of pointing which is social communication.

And in records, or when parents report their observations, if you ask the question did your child point, yes. You are likely to have a yes. But if you start to say give me examples; in which context was he pointing, what type of pointing was present; then you start to make a differentiation about the type of pointing, which is often deficient in autism, but which preserve another type of pointing, which is what I said.

So I'm just saying -- and the same for bringing the shoes, all sorts of gestures. They can be used functionally to express needs. What the quality that we want to see, and that we evaluate,

even retrospectively, is whether or not they are used in an, in a sort of toing-and-froing manner with the partner of the interaction. This is the key aspect which defines autism.

Q And certainly, Mrs. King talked about interactions that she had with Jordan. You recall her testimony about specific instances when he would want to play, he could encourage her to play, and he would see whether she was responsive or not. I mean, all of these things she testified to.

I didn't see anything in your report, and I didn't hear anything on direct either, indicating that Jordan was deficient in these sort of the nonword communicative skills. I certainly didn't, like I said I didn't see anything in the section of your expert report.

So are you claiming that Jordan had poor-quality social communication skills apart from word count?

A No. It's hard to gauge. What I'm saying is that at age 12 months, he seemed to have five words to communicate already in context. So if so, you would expect that this child, in the next six months, would have developed more language.

Q Okay. And you say that he didn't. And if

you look, it's paragraph 138. And there's a sentence that begins, "There is not much evidence." There is not much evidence; you can highlight that, and just that entire sentence.

A Yes.

Q And keep going, please, on the highlight.

Now, when you wrote your report obviously you hadn't heard Mylinda King offer any testimony. Do you recall, in her testimony, that she described Jordan using additional words between the ages of 12 months and 18 months?

A Not precisely.

Q And when you say that his pediatrician's notes are remarkable for their lack of reference, it sounds like you're saying because the pediatrician wasn't keeping track of the number of words that Jordan had, that we can infer from that Jordan was not progressing. Is that what you mean to say there?

A I probably should remove that, because I agree with you. Usually in a pediatric record you would not have, at the beginning of language development, consistent documentation of progress.

But often the pediatricians note babbles, first words, and I didn't find evidence of that in the pediatrician's notes. So I probably used that

indirect type of evidence to support it, but it's not a strong statement what I make.

Q Right. And in fact, at his 12-month checkup, he was noted to be babbling. And so it's more likely that a pediatrician would have noted the absence of words, affirmatively noticed the absence of words in a child who had been babbling. That's a better inference that one could draw.

A I don't think, my experience is not consistent with that. We have a lot of children who do not have any words by when they should have them, and the pediatricians do not document that always. They wait.

Q In this 12- to 18-month window, do you recall how many visits he made to a pediatrician?

A No, not exactly.

Q One of the visits was an emergency room visit for a high fever. Do you remember that?

A Yes, I think I've seen that. Yes.

Q So if a child is being treated for a high fever and a viral infection, and is febrile and lethargic, it's not surprising that a pediatrician wouldn't be making notes about how many words that child has or doesn't have, correct?

A Yes. That's mentioned in my report in

section 133.

Q Now, if we go down to the bottom, there is a sentence that begins, "Although it appears likely." If we can highlight that entire rest of the page.

There's a phrase in here that says, "It is probable that his development was not normal before the loss at 18 or 20 months of age."

In the preceding paragraphs, the only indication that I saw that would support that is the statement that you've already said you shouldn't have put in there, about his pediatrician not noting additional words.

A No.

Q What is the basis for saying that it is probable his development was not normal before 18 months of age? What's the basis in the evidence for your making that statement?

A It's trying to combine all the information which comes here and there in the record. And if you look at what you started with, which is when the mother completed a questionnaire, by the end of my section 137, when he was 26 months of age, she is then asked to document the language development in her child. And what she says, he used single words around one year of age, then stopped.

So he clearly used some words. And what we know is that just a few words, not complex sentences. And that it doesn't seem to have progressed in language development up to the point of losing more complex language.

Q But my question is, where in the evidence, where in the record can you point to evidence that he did not develop more than those five or six words between 12 months and 18 months? Where can you document that in the record here?

A Well, again, I assume that a child who starts single words, and has five or six words by age 12 months, would have developed more words, combinations of two words by age 18 months. And there is no reference to that in, at the time of the loss. The loss is described as a loss of a few words, and that's all.

So there seems to have been no progression in the complexity of language structures between 12 months of age and 18 months of age. These are single words at the beginning, and single words which were lost. So it doesn't seem to be really following the course of language development over a six-month period, and the child was already having five or six words.

Q And even though Mrs. King said he did develop more words between the age of 12 and 18 months.

A Oh, he might have developed more words. Again, the issue is whether or not the quality of the use of these words was communicative, spontaneous, and not solely used to express need, for instance. Which would be a typical -- there is, that type of pattern of language development and loss of a few words is quite prototypical of what I see in my clinic all the time. It's not something which is unusual. So the loss of skills occur at the age, 18 months is often the age at which actually parents report the loss of skills; 16 months, 18 months, 20 months. And usually these are a few words which have been there for several months, with a lack of progress in language complexity and communication, reciprocal communication, in the months which proceed.

So you have a sense that there has been a sort of progressive onset of symptoms, and then a loss, which is usually accompanied with other symptoms.

Q Now, there are two other primary domains that you'd be looking at. We're done with this particular page, Scott.

There is, we've been talking about communication. I also want to talk about social reciprocity. I didn't see any discussion in your report that directly addressed, at least that I saw explicitly, the social interactions that Jordan was having before 18 months of age. I mean, obviously you do talk about things that happened at 20 months and 24 months and 26 months.

Did you see anything in the medical records, or hear anything from Mrs. King's direct testimony, indicating that there were social, deficits in social reciprocity in Jordan before the age of 18 months?

A It's very hard, it's very hard to actually assess again the quality of the social interactions. If I recall well, she mentioned -- and I don't know exactly the timing of it -- but that he welcomed his sister. He has a younger sister, Maya, that he kissed at the beginning. But then she also mentioned that he was ignoring her on a number of occasions.

And I don't exactly know, I think it was around 14 or 15 months of age. You know, that sort of thing --

Q Let me clarify. Fourteen or 15 months of whose age?

A Of Jordan's.

Q Because Maya was born I believe when Jordan was 15 months old. And so Jordan would have been at least 15 or 16 months old before he would have had any opportunity to interact with his sister, correct?

A Yes. I am sure she was describing the time when the baby came back at home. But it's just noted in my notes from the audioi of the testimony of Mrs. King, so that's something which might be a flag. But it's not a definite information either, I agree.

Q And certainly there's nothing that you can point to specifically that happened before Jordan turned 18 months old that would indicate he had deficiencies in the social reciprocity domain. Because again, I didn't see any that were described in your report.

A No. Because you would not ordinarily find that in medical records. I mean, descriptions of social reciprocity would be, or social interactions would be unusual, and their quality would not be usually assessed from medical records.

Q So the only thing we would have to rely on is Mrs. King's testimony. And there's no reason you would have to doubt the veracity and the truthfulness of her testimony, correct?

A Yes. And also the video, which I reviewed,

which I don't think would change my opinion that there is a likely progressive onset before --

Q I'm sorry, I couldn't understand the last.

A That there is a likely progressive, gradual onset of symptoms up to the age of 18 months.

Q And when do you see that in your opinion as beginning? When did that gradual onset of symptoms actually begin, in your opinion?

A I would have really to be careful about dating that. It's very hard. But I need probably to go back to my notes, if you will, my notes of the videos if you want me to go back to that.

Q Well, it's just --

A I seem to recall that around 15 months of age, 16 months of age, there were some observations that suggested that he was not really responding to his mother easily or spontaneously. He seemed to be more absorbed it was a very gradual change. And you could see as well that, for instance, when he was 10 month, 12 month, he was a child with very good eye contact, smiling, responding. And you see that very subtle change in his social functioning, in terms of becoming more serious, giving less eye contact, responding less well.

The timing of that I need to check on the

video, if it's critical. But I think it's, you know, we could all agree with that. It's not --

Q Now, there is another domain that involves play, imaginative play and play with toys. You recall Mrs. King testifying that well into Jordan's second year, he played very appropriately with toys. The tool set, and he would actually use tools as tools, helping his father build musical instruments. Do you recall that testimony?

A Yes, yes.

Q Do you recall that continued well into his second year, at least up to the age of 18 months, correct?

A I don't recall that in particular, but I --

Q And do you recall that she testified that at some point after that, he stopped playing with toys appropriately; and instead of using tools as tools or trains as trains, would line them up and sort of fixate over those objects. Do you recall that testimony?

A Yes. And he drove over and over in a repetitive fashion, and he was starting humming, and, yes.

Q I was just going to get to that.

A Tiptoe walking and --

Q Right about that same time, these symptoms of stereotypical behavior emerged, again some time after 16 or 18 months of age. She described that in a sequence actually beginning at age 18 months and going to age 19 months. She described the sequence of some toe-stepping, and then hand-flapping, and then to the point that, you know, going down the slide he would very vigorously flap his arms.

Do you recall she described that as happening between 18 and 20 months of age?

A Yes, that's consistent with my notes.

Q And there is nothing in the record to indicate that any of those behaviors were apparent before that 18-month, roughly 18-month time period.

A Yes, I agree.

Q So it's fair to say that Jordan King actually developed skills in all three developmental domains and then lost those skills, correct?

A Yes. Yes. Yes, he had skills in terms of play and social interactions and communication that he certainly lost at one point. And again, that doesn't mean that before the loss was obvious that he was absolutely developing normal. I think that would be an inference that I would not put forward.

Q Now we're going to talk about William Mead's

case.

A Yes. Can I also just maybe, for instance, just in terms of the quality of the language with Jordan. There was this note by the father, I think it's the father, who says in written documentation in the record that with hindsight, when they looked back, that he had words by 10 or 12 months of age; but he was never a talker.

Q Well, he actually, that was the comparison he made to his sister, Maya.

A Yes.

Q And you also recall that Mrs. King testified that Maya was somewhat precocious verbally. Do you recall that?

A Yes, yes.

Q And so it's not necessarily a sign that a child is abnormal or slow in his or her development if they are not keeping up with the precocious sibling. I mean, that's not a fair conclusion to reach, is it?

A Yes. We would have to see if she was really precocious. Girls tend to speak earlier than boys in general, so that would not be a --

Q I just want to make clear, that's what, what you're talking about, that was the context where it came up. It was a comparison of Jordan to his sister.

A Yes.

Q And looking at where they were at a particular age.

A Uh-huh.

Q And so girls speak more at that age, so you wouldn't expect Jordan, in comparison, to be speaking as much as she did. And they also described her as particularly precocious verbally, right?

A Yes. It can be all good. Just I think it matches my clinical experience when you see patients and parents at age two or three, when the full picture emerges. Then parents make retrospective assessments of very subtle difficulties that they did not pick up at the time, because it's very subtle. And they say now that I know, so I remember when he was pronouncing his first words, they were actually unusual words, or they were said in a sort of noncommunicative way, or there was no, it was not directed at me.

So there are very subtle abnormalities in the social communication of young children which are reported with hindsight by parents, once they know that the difficulty --

Q Oh, I understand that. And that's what you're telling me about other cases. But what I'm asking you is about this case. And that is not what

Jordan's father described, and that is not what his mother described, is it?

A That's what the father wrote in the note. He said he was never -- you'll have to check on --

Q He described this whole, the lack of --

A He said he was never a babbler.

Q Yes.

A That's to be, he was never a babbler is a consistent description of the children who develop with autism when they are infants. They often do not babble.

Q And I was just trying to distinguish where your commentary picked up, and where Mr. King's note in the record left off and where Mrs. King's testimony left off. All they said was that compared to his sister at the same age, Jordan was not a babbler. That's all that the record says, correct?

A It's correctly said, Jordan was never a babbler, full stop. Then it followed his vocalizations were fairly limited compared to her articulations. So --

Q To her articulations, yes.

A Yes.

Q Okay.

A So then the comparative statement.

Q So that's all I was trying to establish, who said what, and what was your commentary versus the parents' testimony and the note in the records.

So now we will talk about William Mead. Now, William Mead, you would agree, had a pretty fair repertoire of words by the time he was 18 months old. Would you agree with that? That he was using two-word phrases? Do you recall George Mead testifying that he would say "up, Daddy," "down, Daddy," "let's go?" Do you recall that testimony?

A Yes. I remember that Dad said that he was even speaking in three-word sentences at age 12 months, which is quite difficult to actually believe. And again, I want to point out that retrospective parental accounts are notoriously difficult to evaluate, particularly in terms of the timing.

So I'm not saying more than that. It's not a comment about Mr. Mead's testimony. But it seems that in the document about William, we see sometimes he had 60 words that he lost, and then in other areas it's more like much more simple words that he had. So there is inconsistency, both of the extent to which he had fully developed language at the time he lost his skill; and there is also inconsistency about the dates. The dates in the records, and these are

prospectively recorded times, inconsistent in the medical record.

And even in the testimony now it says something else. I think the whole picture, in terms of timing of these milestones in terms of getting new skills or losing some skills, is very complex. That means it's a complex issue for us as clinicians and researchers, and I think the whole picture is not very clear. That's what I want to say.

Q And in reading your expert report, the focus that you seem to have were what you saw as inconsistencies in the record between the age of 18 months, and between the age of roughly two-and-a-half years of age. And trying to place -- just the sense I got from your report is that you were trying to figure out whether his regression would be placed at 18 months or 24 months or 27 months. Is that a fair summary of this couple of pages devoted to William?

A Yes. Could you point me in what specific paragraph?

Q No, I just wondered if that was your general sense. Because I don't want to just read the whole report to you out loud.

A No. I think when I was trying to evaluate the timing of it, I don't -- I agree that there is a

loss of skills, a change in William and a loss of skill. That's not an issue.

The issue is when it happened, and was there a discreet time when the losses could be evident? Or was it more a gradual process, where there was like lack of progress in critical skills, followed by the loss of some skills which were acquired before? So I think that that is very difficult to evaluate, as it is very difficult to evaluate the actual timing of that loss.

So, you know, in some areas, in some records it mentions the summer of 2000 as being a critical time when the parents really realized. So that's really upper limits in terms of their realizing the difficulties. Then you can go back. There is a mention, which unfortunately is not very well documented, that he went to daycare, probably at the beginning of the school year of 1999, when he was 16, 17 months. And he was asked to leave the daycare because he was not fitting in. And that's a strong indication that he was not normal. And that seems probably to have occurred before the 18 months or two years of age.

Q And on that point, yes, I would not -- what I want to focus on is the 18 months. Because I think

Mr. Mead did testify that even in looking at medical records, he said looking back now, retrospectively, we, speaking about himself and William's mother, he said we now realize that there were some signs at the age of 18 or 19 months. I mean, he said that on direct.

So he acknowledges that things were beginning to appear around 18 or 19 months. So I would offer that to resolve any dispute about whether Mr. Mead is claiming 27 months or 24 months. He is saying retrospectively that 18 months is when he first, he and William's mom first saw problems. Do you recall that testimony from George Mead?

A Yes. Yes.

Q Have you been able to identify anything from the medical records indicating that William Mead was deficient in any language or communication skills before the age of 18 months?

A Before the age of 18 months?

Q Correct.

A I don't think so.

Q Are you aware of anything in the medical records or in the testimony of Mr. Mead indicating that William Mead was deficient in any of the social skills, or deficient in social reciprocity in any

demonstrable way before the age of 18 months?

A No, not in a -- no. Based on my notes, no.

Q Are you aware -- sorry, were you done?

A Yes, yes.

Q Are you aware of anything in the contemporaneous medical records or the testimony of Mr. Mead indicating that William was deficient in the area of play, behavior, or imaginative play before the age of 18 months?

A Nothing in his testimony.

Q So you can't identify anything in Mr. Mead's testimony or in the medical records indicating that William Mead was abnormal in his development before the age of 18 months.

A Yes. But again, the fact that it's not there doesn't mean it was not there. And --

Q Well, part of your testimony in your report is that it might not have been there. So I want to know --

A No, no. Based on medical records, I didn't see any evidence of that. I agree.

Q And then based on his testimony, you didn't see any evidence of that, either.

A No. But I think the video was showing a slightly different picture.

Q Did you testify about the videos?

A No. But I reviewed them all, and I can look back at my notes. I am pretty sure that there are clips where William's interactions are not particularly reciprocal, and the amount of language which is produced by him is actually extremely limited.

Q And this would be in video before he turned 18 months of age?

A Oh, yes.

Q Is there any doubt that William Mead lost skills in all three developmental domains at some point between the ages of 18 months and 27 months?

A No, I don't dispute the fact that there was a loss of skills. For instance, the videos show that he had a couple of words that you hear, but that's about it. So there is about 12 months of age, I heard two utterances, the spontaneity of which is uncertain. And the rest of it I really, through a lot of footage, didn't hear language from that boy in circumstances where you would have expected more language to be produced to communicate.

So that doesn't really contradict the fact that he might have lost skills, and changed and developed autistic symptoms, and lost social skills

and play skills later. I agree with you.

Q And for William Mead, would you say that he definitely regressed?

A There was a loss of skills, yes. Based on what we are discussing today, I have no problem with that.

Q So you have no problem saying that William Mead definitely regressed.

A Well, what do you mean by definitely regressed?

Q Well, it's a term that I heard you use earlier today.

A Yes. But there was a technical term of the ADI. So that he experienced a loss of skills, I do not dispute that, that's for sure. That's what I say. That his development was normal before, I'm not sure.

Q But you would say he not just lost skills, he definitely regressed. And you agree with the autism diagnosis.

A Yes.

Q And the same with Jordan King.

A Yes.

Q He definitely regressed, and he has an autism diagnosis, and you agree with that diagnosis.

A Yes. They both lost skills in the course of

their second year of life, closer to the fourth semester of life.

Q I'm sorry, closer --

A Closer to the second part of the second year of life, which is often what is seen. But you have a sense, when you review the record and you review the tapes, that there was a gradual onset of symptoms over time, over a period of time. And then a time where there was also a loss of skill.

MR. POWERS: No other questions right now.

SPECIAL MASTER VOWELL: Redirect?

MS. RICCIARDELLA: Yes, ma'am.

REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Dr. Fombonne, Mr. Williams on his cross-examination was talking about thalidomide and terbutaline, some of the known medical causes of autism. And he said that the number was so small, and I think you acknowledged that the number of those cases, cases caused by terbutaline or cases caused by thalidomide, were so small that they may not be picked up by epidemiology. Do you recall that line of questioning?

A Yes.

Q But in those cases, can we identify a

specific phenotype, a specific phenotype that we know what caused that autism?

A Yes. In the case of congenital rubella, yes, you can identify symptoms of congenital rubella, in addition to symptoms of autism.

Q Do we have that same ability with regard to regressive autism? Can we identify a distinct phenotype of regressive autism, as compared to all other autism?

A No. As I said before, and Dr. Lord said, it's not a phenotype which is associated with clinical characteristics, or familial characteristics, or course or response to treatment. The factors that we usually use again in psychiatry to validate different types of syndromes.

Q There was also a lot of questioning with regard to prevalence rates and incidence rates. And there was some confusion.

Would you please state again what is meant by the term "prevalence rates?"

A Prevalence is just that it's a photograph of a particular population at a particular point in time, and then you count the number of the people in the population, and that's your denominator. And then of this population, you count those who were affected by

the disease, and then you put them in the numerator. So you can have five persons out of 100 who have blue eyes; the prevalence is five percent. And that's the way it is. So that's prevalence.

Q Is it a snapshot in time?

A Yes. There is no, again, no passage of time. It's an instantaneous photograph of a situation at a given point in time.

Q And is that different than incidence rate?

A Yes. That's the key difference, is that incidence involves the passage of time. So you start here, and you finish there.

And in this interval you count the number of new cases of disease in the particular population, which is predefined at the beginning of the study period. That's the way you compute incidence.

One of the confusions is that incidence can be expressed in complex incidence rates, where you have complex denominators which are difficult to interpret intuitively like person-year denominators. That's pure incidence rate.

There is a type of incidence rate which is like a prevalence because it's a proportion. And let me just explain, I don't know -- well, if you then follow 100 children from birth up to age 10, so you

have the passage of time; and then you count those who develop a certain disease. So you can express the incidence of this disease as being 10 out of 100, which is your starting point. So you have 10 percent of this cohort which, at age 10, has the disease. That is an incidence figure which is expressed as a proportion, like prevalence rates.

Hence, some proportions refer to what we call cumulative incidence, and some proportions refer to prevalence proportion prevalence rates. That's why you would see in the graph sometimes percent as cumulative incidence. That's, I'm sorry, it's a bit technical.

Q But studies, a prevalence study is different from an incidence study, is that correct?

A Yes.

Q Okay. And you were asked some questions about the Schechter and Grether study. Was that an incidence study or was that a prevalence study?

A No, it's a prevalence study.

Q And what conclusions did the authors of the Schechter and Grether study come to with regard to prevalence of autistic spectrum disorders in the state of California?

A Well, in the state of California? They said

that prevalence is 46.5 per 10,000 in the group of children which were age six in their study, which is somewhat of an underrestimate compared to other population rates. But otherwise, they provide proportion of the new notifications in the age group three to five. So these are prevalence which are adjusted over time.

Q And what do you conclude from that study with regard to the prevalence rate, vis-à-vis thimerosal-containing vaccines?

A That as the authors conclude themselves, they are very clear in their conclusions. They are saying that the phasing out of thimerosal-containing vaccines in California has led to no dip in the prevalence rates in the age group where we should see it.

So if there was a connection, they should have seen a decrease in the prevalence after 2004. And the reason why is that they could have seen it is that, in fact, these numbers are high. As I said before, the DDS database adds I think about 3,000 new cases per year in the system.

So if you have a risk factor which contributes to even 10 percent of the disease onset and it is removed, you should see a dip, whatever is

the trend should see a dip of 10 percent, and the trend would continue. But this was not seen.

Q Now you were also asked a series of questions regarding your 2001 study that you published with Chakrabarti, filed as Respondent's Master List 147, that looked specifically at regression. Do you recall that line of questioning?

A Yes.

Q Now, was the focus of that study whether the children were entirely normal? Or was the focus of that study whether the children actually had a regression?

A I'm sorry, could you repeat that question?

Q The focus of that study, was it whether or not these children were entirely normal before, before they developed autism? Or was it whether or not they actually regressed?

A Oh, no. The focus was just in estimating the proportion in two samples of children experiencing loss of skills in their development, that's all. It was not looking at definite regression after normal development. This was not at all the focus.

The focus was just documenting a loss of skills in their development, using an operationalized definition.

Q And there was a line of questioning as to what you meant by the word, phrase, "definite regression." What was meant by the phrase "definite regression?"

A It was a higher level of definition. So for definite regression, again, definite regression terminology does not, has nothing to do with clearly regressive autism that we have been talking over the last few days. It was just, it's a way to say the child has lost his skills in a way which fulfills entirely the stringent criteria that you impose to document that loss.

So he was using at least five words, spontaneously, daily, with meaning, for three months, and then lost them for at least three months. That's what it means. That's a purely descriptive term.

And probable was for those instances of loss of skills which are obvious, but not meeting the stringent criteria.

SPECIAL MASTER CAMPBELL-SMITH: Let me just interrupt while we're on the topic. That's a question that I had was you're referring to the standards, their meeting these stringent criteria. Is that to improve the concept of inter-rater or reliability? That when you identify this definite set of loss,

every professionals who refer to that and use these skills would know exactly what you are talking about. Because everybody is consistently following or adhering to the same set of evaluation criteria.

THE WITNESS: Yes. At the time, it was really to put clarity on this phenomenon and try to measure it in any sort of way, in a way which could be reliable across raters. We previously did not have any ways to do that.

But now with all the studies on regression that's evolved, and have shown that we need actually to be less stringent. And if we are less stringent -- for instance this is too strict of a criterion, because you have some children who have loss of quality in their babble, for instance. They suddenly change, they stop babbling. They babble well up to nine months, and then something, their gaze is starting to be fixated at objects, and they stop babble. They babble suddenly in a very monotonous way.

So there is a change in quality, which is like a loss of skills. But these kinds of early onset loss of skills or transformations would not be captured by our more stringent definition.

So now the work of Dr. Lord and others is

trying to be much more refined, documenting which skills are lost, and becomes much more complex. And we see that as not being a categorical phenomenon. It's really a continuously distributed phenomenon. So there are different types of loss of skills at different times in the development, and it's how we are now concentrating this developmental trajectory.

SPECIAL MASTER CAMPBELL-SMITH: Thank you. Pardon me.

MS. RICCIARDELLA: No problem.

BY MS. RICCIARDELLA:

Q And you were also asked by Mr. Powers a series of questions with regard to the two individual little boys who comprise this litigation.

With regard to Jordan King, you were asked about loss of skills, onset. Is Jordan King's autism any different or unique from the children that you see in your clinic in Montreal?

A No, not at all.

Q Is William Mead's autism different or unique compared to the children that you see in your clinic in Montreal?

A No. Based on the medical report of my review of the videotapes; it's very much the same.

MS. RICCIARDELLA: Thank you.

SPECIAL MASTER VOWELL: No recross?

MR. POWERS: I'm checking with my colleague.

SPECIAL MASTER VOWELL: He's shaking his --

MR. POWERS: We're both shaking our heads. No, nothing else from Petitioners, thank you.

SPECIAL MASTER VOWELL: All right. Do any other of my colleagues have any questions?

SPECIAL MASTER CAMPBELL-SMITH: It's been answered.

SPECIAL MASTER HASTINGS: Let me just ask one, Doctor. Most of my questions actually have been answered. Pages 42 and 43 of your report, if you could turn to them. And actually, on page 42, at the beginning of paragraph 105, you talk about an ecological study in Quebec. It wasn't clear to me when I read the report which study you were talking about. Is this a published study?

THE WITNESS: Yes. That is the study I presented as published in Pediatrics in 2006.

SPECIAL MASTER HASTINGS: Okay, thank you. That's all I have.

SPECIAL MASTER VOWELL: All right then. Dr. Fombonne, I believe you're excused.

(Witness excused.)

SPECIAL MASTER VOWELL: Counsel, I take it

we have nothing else for today.

MR. POWERS: That's right.

SPECIAL MASTER VOWELL: Do we need to discuss anything off the record before we all break then?

MR. POWERS: No, ma'am.

SPECIAL MASTER VOWELL: All right. Then we'll reconvene tomorrow morning at 9:00 a.m.

(Whereupon, at 4:53 p.m., the hearing in the above-entitled matter was recessed, to reconvene at 9:00 a.m. the following day, Thursday, May 29, 2008.)

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REPORTER'S CERTIFICATE

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CASE TITLE: King and Mead v. HHS

HEARING DATE: May 28, 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 28, 2008

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