UNITED STATES
COURT OF FEDERAL CLAIMS

THERESA CEDILLO AND MICHAEL CEDILLO, AS PARENTS AND NATURAL GUARDIANS OF MICHELLE CEDILLO,	)	
Petitioners,	)	
v.	)	Docket No.: 98-916V
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

Pages: 2496 through 2869

Place: Washington, D.C.

Date: June 25, 2007

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IN THE UNITED STATES COURT OF FEDERAL CLAIMS

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SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

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

Monday,
June 25, 2007

The parties met, pursuant to notice of the Court, at 9:02 a.m.

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

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C O N T E N T S

WITNESSES:	DIRECT	CROSS	REDIRECT	RECROSS	VOIR DIRE
For the Respondent:					
Eric Fombonne	--	--	2500	--	--
	--	2586	2724	--	--
Diane Griffin	2739	2798	2860	2866	--
	--	--	2867	--	--

E X H I B I T S

PETITIONER'S EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
15	2639	2639	Newschaffer study
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P R O C E E D I N G S

(9:02 a.m.)

SPECIAL MASTER HASTINGS: Good morning to all. Today we continue with the government's case.

Mr. Matanoski, who will be your first witness?

MR. MATANOSKI: Dr. Eric Fombonne to testify about epidemiology.

SPECIAL MASTER HASTINGS: Okay. Very good. Dr. Fombonne, please take the witness chair.

Dr. Fombonne, would you raise your right hand, please?

Whereupon,

ERIC FOMBONNE

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

SPECIAL MASTER HASTINGS: Okay. Ms. Ricciardella, please go ahead.

MS. RICCIARDELLA: Thank you.

FURTHER REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Welcome back, Dr. Fombonne. Good morning.

A Good morning.

Q You're an epidemiologist, correct?

A Yes.

Q What is epidemiology?

A There are many definitions of epidemiology, and the most common one is that it's the science which is the study of the distribution of disease in human populations and the study of factors which influence that distribution.

Q Now, there's more than one type of epidemiologic study design. Is that correct?

A Yes.

Q What are the different epidemiologic study designs?

A Well, there are many designs, but there are two major designs, which are the cohort study and the case-control study.

The cohort studies are also referred to as incidence studies, and these are really studies which compare the new onset of a disease in two groups of subjects which are contrasted, and the groups are defined by the fact that they are exposed to an exposure, which is studied by the epidemiologist, and there is a group which is unexposed to that exposure, and then by following the exposed and unexposed subjects over time you can measure the incidence of a new disease in both groups and then compare it.

If it is comparable or equal then the relative incidence will be one and there will be no effect of the exposure on the incidence of the disease.

The second design is referred to as a case-control study, and then you look at the same question, but the other way around. In that design you start with a group of subjects who have the disease that interests you, and then you select a group of controls and then you work retrospectively in each group to measure their past exposure to particular events or biological difficulties in order to assess if the exposure was higher in the group of cases when compared to the control, and then that translates into an odds ratio, which is a measure of relative risk.

Q And the third study is a prevalence study. What is that? What is meant by a cross-sectional study?

A Prevalence studies are referred to also as cross-sectional studies. These are studies which in a sense are taking a photograph of a given population at one single point in time and then you just go and assess every person in this sample, in this population, and try to identify who is diseased, who is not diseased and who has the particular

characteristic that you want to relate to the disease.

There is no passage of time here. You just look at the disease studies and the exposure studies simultaneously.

Q And the final type of study is the ecological study.

A Yes.

Q What is that?

A The fourth kind of design which would be used subsequently this morning is ecological studies. In these studies, as opposed to the first two designs, we look at rates of a particular disease over a period of time, for instance, if we want to relate to rates of exposure over the same period of time.

To take an example, one could ask in a given state if there is a relationship over time between unemployment rates and suicide rates, for instance. There could be evidence that there is a positive correlation showing that as unemployment rates go up suicide rates go up as well, and that would be some kind of evidence that there might be a relationship between the two, although the type of inferences which can be made from ecological studies is much less strong than what we can make from the first two designs.

The reason is in these ecological studies we only have access to aggregated data, and we need to know at the individual level who was exposed and who was actually diseased, so there could be some spurious correlations which arise from these ecological studies.

SPECIAL MASTER HASTINGS: Dr. Fombonne, before you go on I just want to go back here.

THE WITNESS: Yes?

SPECIAL MASTER HASTINGS: As with previous witnesses, Dr. Fombonne has some slides to go with his testimony here. We've got paper copies of that. Let's mark this as Respondent's Trial Exhibit 21.

We went over Slide 1. The four types of epidemiological studies that he talked about were in Slide 2.

I'm sorry, Ms. Ricciardella. Go ahead.

MS. RICCIARDELLA: That's okay. Thank you, Special Master.

BY MS. RICCIARDELLA:

Q Doctor, there's a difference between prevalence rate of a disease or disorder and incidence rate, correct? Now I'm on Slide 3.

A Yes. When we conduct studies we measure the occurrence in populations in different measures of

these occurrences.

One is called prevalence rate, also referred to as prevalence proportion in fact, and it's just when you investigate the particular sample you can calculate in a given study what is the proportion of subjects in that sample who have the disease, so it's a simple proportion which varies from zero to one and which tells you how many people in this sample of this population have the disease.

Attached to this proportion you can calculate a coincidence interval to provide some measure of a certainty about the true parameter and the population.

Q What are incidence?

A That's just prevalence. It's a static measure. Again, it doesn't give you an idea about a new onset of cases.

Then in terms of incidence there are two different ways to calculate incidence. The first one is called often cumulative incidence, and this is for designs where you start from time one, for instance, where you study people who are all free of the disease at the start of the study, and then you follow them up over time.

So you follow them up, for instance, five

years. After five years, a certain proportion of this initial pool of subjects will have developed the disease, and that proportion would be called the cumulative incidence. It is a proportion like prevalence so it has no units. It's attached to a 95 percent confidence interval as well, but of course this cumulative incidence will vary according to the length of follow-up of the study.

If you follow up people for five years you can have like 10 percent would develop the disease over that period of time. It is important to relate the cumulative incidence to a particular period of time.

If you extend your follow-up period to 10 years, your cumulative incidence can only go up, and here may be at the end of 10 years of observation maybe 15 percent of people in that particular initial population or sample who have developed the disease. So it is a proportion, but it's dynamic in the sense that it really measures the number of new onset of the disease over a given period of time, so that's cumulative incidence.

Then there is another way to calculate incidence which is more complicated, which has less intuitive meaning, which is called incidence rate.

It's for studies where we look, we observe, populations which are usually in the dynamic state so there are people who come in, people who come out, people who die.

Every person in this population is observed for additional periods of time, so we need to take into account how many people are observed during this period of time and how each individual is observed during that study period.

Some could be observed for a short period of time because they go and disappear. Some join the population. They would have shorter periods of observation. We take into account basically how many people have been observed for how long each time, and this is what constitutes the denominator of this incidence rate.

The numerator is made of the number of new onsets of the disease over a period of time, so that's why the denominator is expressed usually in person years and the unit of incidence rate is in fact the inverse of times rate. It's a bit difficult to understand.

Just to give you an example which is more easily understood, suicide statistics are often expressed. They are incidence rates. If you follow

the press, which I think suicide rates in the U.S. for young males age 15 to 20 or 15 to 24 are probably in the vicinity of 20 per 100,000 per year, so you relate your number of events, 20, to the size of the population and duration.

Instituting that case, it's easy to understand. It means that if we could observe 100,000 individuals in this age group over one year, we would expect to have 20 persons who would commit suicide. That's a case which has a direct interpretive interpretation, but sometimes it's a bit more complex to understand. That's the measure of incidence.

Q Are most epidemiologic studies of autism looking at incidence rates or prevalence rates?

A In the field of the epidemiology of autism, most of the studies have been prevalence studies. Prevalence studies again are studies which are static. There is no passage of time.

There are a few incidence studies available, but they are not particularly well designed so most of what people have relied to in the field of autism epidemiology has been prevalence studies.

Q Doctor, what has research shown to be the current prevalence rate of autistic spectrum disorder in the United States?

A Well, in the United States there were historically a paucity of studies to investigate this question, and over the last seven years there has been a major effort to generate good population estimates for autism spectrum conditions in the U.S.

It started with a CDC study in New Jersey, which was published in 2001. There was another major effort in Atlanta published in 2003. Then the CDC actually, concerned with rates of autism and the fact that there were no U.S. data on that, started in early 2000 I think to develop a monitoring program for autism epidemiology in the U.S., and just this year in February they released the first results of two major surveys of autism spectrum conditions in the U.S.

What they did was to look at children who were eight years old, and they looked at them in various states in the U.S. There are 14 states involved in this monitoring project all concentrating on eight-year-olds.

The method which is used to identify cases in these states has been quite standardized. It's similar across states, so the goal is really to generate good population estimates for the U.S. on a large scale.

Q I think we have that. That's Slide 5.

A That was Slide 4, and now we are on Slide 5, yes.

They released earlier this year the results of two major surveys, and you see on that slide just one of them. In the same report, which is I think the *Mortality and Morbidity Weekly Report*, they released prevalence estimates for eight-year-olds in 2000, and in 2000 the rate was 6.7 per 1,000 or 67 per 10,000, the same figure.

And then they monitored the same or similar states two years later, again looking at eight-year-olds, and this is what you see here. The average prevalence in the children, the eight-year-olds, in 2002 in 14 states, the average figure is 66 per 10,000 or 6.6 per 1,000. That is what that graph shows.

The graph shows actually you can see in the vertical bars the rates which are for each state. I think it's important to actually take a minute to look at the viability. The actual prevalence estimates for each state appear in these little squares, which are orange squares.

As you can see, on the right-hand side the white column is the column which is for New Jersey. You can see the rate in New Jersey is actually I think it was 107 per 10,000. In other words, actually in

New Jersey in eight-year-olds in 2002 the rate was 1.07 percent of the population had an autism spectrum disorder, 1.07 percent. That's the highest rate that we see.

Then you see many states who show more into the 60 to 70 per 10,000, but you see also on the left there are some states which have quite a low population estimate like, for instance, the state of Alabama is standing out as being very low, so you have the rate here, which is like 32 or 33 per 10,000.

It's important to therefore recognize that the average figure on the top is an average. It's an average across 14 states. If you look at across state viability, it's quite high. You have a threefold variation in the rates between Alabama and New Jersey.

It's important to recognize because this is at one point in time, but nobody would say that this date, for instance, supports that there is an epidemic in New Jersey or something in Alabama which protects you against autism.

This shows already at one point in time how you ascertain cases in a population in fact in your prevalence estimate, and it varies a lot across regions in the same country at the same time.

Q So, Doctor, you would agree that prevalence

rates for autism are higher than in years past?

A Sure. The two rates which I quoted from the CDC study are actually highly consistent with the rates which have been published in the literature over the last six or seven years.

I know at least of about 12 published studies which show rates which are consistently around 60 to 70 per 10,000, which is probably the best estimate that we have today. These studies have been done by different groups of investigators using different methods. They come from the U.K. They come from Canada, from the U.S -- there are multiple studies now -- and also from Scandinavia, the Faroe Islands. You name it, there are multiple replications of these findings in recent studies.

So that's the recent picture worldwide. Now if you ask compared to what it was like 30 or 40 years ago, yes, of course it's higher. In the past, we recorded rates initially which were four or five children per 10,000 in the earlier epidemiological studies starting in the '60s and early '70s. Therefore, the prevalence figures that we provide right now are higher than they used to be.

Q Well, then why isn't that evidence that the disorder is increasing in the population?

A Well, it could be evidence that there is an increased incidence of the disorder, but it could also reflect different factors.

One of these factors has been studied, and there is abundant evidence and there are reasons that we understand why the prevalence figures are higher than they used to be. One of them has to do with diagnostic concepts and diagnostic criteria which have changed over the last 40 years.

Q Does the change in diagnostic criteria affect prevalence rates?

A Yes. Absolutely. This is now Slide 6. It shows in the slide the evolution of nosographies, and indeed in 1968 there were basically no provisions made for child psychiatric disorders.

The first really criteria for autism were developed by Michael Rutter in England in 1970. They were subsequently embodied in 1979, in 1975, and then in the U.S. is really started to change in 1980. In 1980 it was the first time that the notion of PDD was shown in the literature.

That was really to go away from previous concepts where up to that point autism was linked up with childhood psychosis. It was very vague the way it was conceptualized. To emphasize the developmental

nature and the early onset of autism, this term of pervasive developmental disorder was coined in 1980s and appeared in *DSM-III* for the first time.

In *DSM-III-R* there is a reorganization and simplification of *DSM-III*, and this is the first time in 1987 that the concept of PDD-NOS appeared. There was no PDD-NOS category before.

Then we move on to *DSM-IV*. *DSM-IV* was released in 1994, and here you have a reorganization of the diagnostic criteria for autistic disorders, PDD-NOS, but also you have newcomers in the classification. Asperger disorder did not exist before. It made its appearance, its entry, in 1994.

These are important changes, and there are actually empirical studies looking at comparing the same clinical material and applying *DSM-III-R* as opposed to *DSM-IV* criteria, and *DSM-IV* criteria led to I think it was a 40 percent increase in the empirical study of children with early diagnosis of PDD compared to *DSM-III-R*, so it's clear that the change in the concepts and then how they are reflected in diagnostic systems have an impact on who meets criteria or not in any study for an autism spectrum disorder.

For the epidemiology, we knew that the best way to demonstrate that came from one study which was

done in Finland. If I could maybe have the next slide?

Q I believe your report refers to it. I'm referring to Respondent's Exhibit P, Tab 97. What did that study find?

A Okay. This is Slide 7. The direct way to estimate how different diagnostic criteria impact on the result is to collect data, and that's what these investigators did in Finland.

They did one study, one survey. They collected their data, and therefore the data do not change or vary. What they did, they applied to this same data different diagnostic criteria to see how changing the diagnostic criteria affects the results.

By using Kanner's criteria, for instance, in this age group they generate a prevalence rate of 2.3 per 10,000, but if they apply the more recent, modern *ICD-10* criteria then the rate is 7.6 on this same survey. There is nothing else which changes but the diagnostic criteria.

So you have here a demonstration that diagnostic criteria can account for a threefold difference or increase in the rates themselves. Of course, it might not be as often the case in other studies, but that's a very clear demonstration that

diagnostic criteria can impact substantially the prevalence estimates in studies.

Q Does case ascertainment assess the prevalence rates of ASD?

A Yes. And this is Slide No. 8. Case ascertainment is when we do epidemiological studies of that kind, we first set a case definition, so we define what it is that we will call ASD or PDD in that study, so that's the case definition.

Then there is another big decision to make, which is how are we going to investigate and find out the cases in this community that we survey. This is called case identification or case ascertainment.

The way it has been done historically in studies is actually not standardized. Because these populations have a large sample size, often tens of thousands of children of a certain age, we cannot go and assess every child. It's not feasible, so we often do screenings first.

The extent to which you screen can vary a lot. Some people send letters or flyers. They again send out to GPs only, doctors only or they send them to schools as well or only to schools, so there are multiple reasons why when we ascertain cases there is huge variability in the design of these studies, and

that in turn can affect the findings and the years of cases in our studies.

That slide is an example of how case ascertainment can impact the rates. You can see there these are four U.S. studies, one done by the CDC in New Jersey in 2000, and then you can see all of them. The point is that it's the same country. They are all U.S. studies. They are all published at the same time, 1999 to 2001, and the age groups are more or less similar.

So what should we expect? If we do four studies at the same point in time in the same country, we should have similar rates. On the right column you can see the rates actually vary enormously. There is a 14-fold variation in these prevalence rates according to these studies.

How can we explain that? The only way to explain that is that there are unique design features of each study which impact substantially the rates. When one looks at those three studies which give rates which are 16 or below, they are all identifying cases based on children who are already known from educational services.

This is a kind of passive way to identify kids that are known in other domains of epidemiology.

So if you just rely on one single source of cases which are going through a particular service provider you will have some of the cases, but you will miss many, so this kind of special identification system tends in all countries to yield a low rate.

By contrast, the first study, which had very high rates as early as 2000, was really going at cases in this community in a very different way. They were using multiple sources of ascertainment. They were very proactive in trying to find cases using different diagnostic measures.

There were multiple reasons, but the degree of activity and associated cases clearly led to that study having a higher rate compared to the other ones, so the point to make here is that case identification or ascertainment in studies varied enormously and that it does affect how much autism you find in a particular survey.

If that is the case, it becomes obviously much more complicated to compare historical studies, so if you have rates now of 60 or 70 per 10,000, as you see, there is variability in studies conducted in that same historical period. It's clear that comparing studies done now to studies done 40 years ago will be plagued with multiple concerning factors

due to design features of studies which are not comparable.

Q Doctor, some people have used referral data from health care and educational providers as evidence that the incidence rate of ASDs are increasing. Is it good practice to use referral data to evaluate incidence?

A No, it's not good practice to use referral statistics or data to evaluate or estimate incidence, and it's not good practice to try to estimate trends in rates of autism using only referral statistics.

Everybody will understand in any medical institution when you develop a service or you offer a service suddenly you find patients. So as a function of how much service you provide, you will create trends in the apparent rate of the disorder which have nothing to do with what's happening in the population, which is what we want to know. That is a kind of illustration, a classic illustration on how service-based data can be misleading.

Q Excuse me. We're referring to Slide 9.

A This is Slide 9, yes. In each slide there's a green square that represents the population. The pink area is those in the population who have the disease who are accessing services.

Assume that there is an equivalent number of dots in each slide and the dots are for each individual who have the disease. So an equal number of dots in both situations, that means that the prevalence in the population is the same. There is no change.

But in the first case on the left, of these people who have the disease, just very few access services. So you have like, I don't know, seven people in the service provider. And then later you have suddenly a high access of services. The disorder is recognized. There is more awareness, more facilitation of access to treatment, and you have suddenly many more people who are in the service provider statistics or data although the prevalence in the population has not changed.

What's happening from the next slide is that there is a transfer from the population pool of cases towards those who are accessing services, and if you only concentrate on the number of dots in the pink area you will generate a trend which is a very, very low access and a high number later. You have an upward trend.

In fact, we must, if I was the attorneys, have access to the population estimates. Unless you

do that you can be misled by looking at how many people are treated in a particular service or identified in a system with an autism category.

These are all what I would call sterile statistics, and that involves Department of Education data or health data, and they are not appropriate to evaluate the trend.

Q Why isn't Department of Education data a good gauge of incidence rate?

A Well, this is one impression from that slide. This is Slide 10. It comes from a paper by Gurney, et al., and it's consolidating numerous data, but the trend that you see is a trend you see in all states or most states in the U.S. and also a trend that you see in England, in Denmark, in Canada, in every country where you have seen trends of this kind. You have this same type of curve.

The reason why is when you see that you could say well, there is an increased number. It can be impressive, but of course these trends do not account for changes that are very important in how we define cases and how children with the disease access benefits.

For instance, in that study we just portrayed important events in terms of diagnostic

concepts and criteria, and you can see that this upward trend occurs at the time where the new conceptualization of ASDs have been embodied in *DSM-IV* and *ICD-10*, and again that happens everywhere.

That's one change in how we conceive and conceptualize autism, but the other thing in the U.S. which is relevant is this IDEA Act, which is the Individuals With Disabilities Educational Act law which was passed I think in 1990.

What is important to note is that in the past, which is before 1990 or before 1991, there was no requirement for U.S. states or educational facilities to report autism as a separate category, so in the Department of Education data autism was actually linked up with a category which was other kinds of impairment in the past.

It's only following this 1990 law that states had to report autism as a separate category, and that started actually in 1993 officially, but particularly in 1994. This is when states had to report autism as a separate category.

That of course means differences when you open up categories, as we will see later. When you create a new category of course numbers would increase because it can only go up. That's for sure. We've

seen that in the other kinds of developmental disabilities over time.

This kind of trend in educational data or other kinds of data cannot be directly interpreted because you never can control or adjust for change in the diagnostic criteria, and also they need to take into account change in the social policy around this particular disorder.

Q Doctor, is there direct evidence that diagnostic practices have changed to explain the higher number of ASDs?

A Yes. Yes. There has been a very important study, which is shown in Slide 11.

Q And I believe you're about to refer to Respondent's Exhibit P at Tab 161. Go ahead, Doctor.

A Yes. In this study by Shattuck published in 2005 is an elegant demonstration that you can have what is called diagnostic switching or diagnostic substitution, and that can explain to a large extent the increases in numbers of children who have currently a diagnosis of ASD.

The average would be actually off, so I'm going to explain that. On this slide you have the dotted line, which is always on the top, is what you would predict would be the prevalence based on recent

CDC studies. The average would be slightly higher up and on this line. The line is at 67, 68 per 10,000. That's the recent figure that we have, and that's what we know is the true population rate, if I can put it that way.

The other dotted line, which is always around 34 per 10,000, reflects a lower estimate of the population rate, which is derived from one CDC study published in 2003 and conducted in the region of Atlanta.

So basically these two lines provide us with a reference range of where the prevalence is based on studies which are available. If one looks at the other lines, the big line which is the thick line in between the other two is the average prevalence based on the number of children in the U.S. across states which are in the Department of Education data recognized as having an autism condition.

If one looks at this trend over time what is important is in 1994 on the left-hand side, and the average is actually not at the right page, but the starting point is an average prevalence of six per 10,000, meaning that in 1994 if we just look at the Department of Education data in the U.S. across all states you would estimate that there is about six

children out of 10,000 who have an autism spectrum disorder condition.

But because we know that the population figure is higher it starts very low and can only go up over time. What's happening at the end of this period, the end point in 2003 of this average rate is about 32. It's not even at the level of the lowest estimate of the reference range which I described before, showing that any trend to increasing numbers in Department of Education statistics is reflecting the fact that these statistics are catching up with reality.

We know that in the population there are many more children, and those who are identified in the educational system as pertaining to the autism category are increasing, but it's still far from being what it should be based on our knowledge of the true prevalence of the disease in the U.S. population. So therefore the fact that it has increased cannot be interpreted as showing that there is an epidemic as it is sometimes said.

Of course, there is also huge variability across states so that you see a line which goes quite high. This is the trend for Minnesota, and there is another state, which is the lowest state in terms of

how many kids are identified, and that's New Mexico, so there is variability across states as you would expect and as I showed before.

But the mean, which is the thick line, shows that the original data showed much beyond catching up with the population figure, and we should predict from this slide that they should increase even more in future years, and that would not be a sign that there is an epidemic. So this author, being aware of that, he asked several questions and basically in four steps tried to try to address this question of diagnostic substitutions.

The other question, this increasing number of children with ASD in the Department of Education data, are they in fact children who were there before, but now they are reclassified in a different category? The first thing he did was to look at the whole I think 48 states that he included in this analysis, and he looked over time between 1994 to 2003.

He calculated the odds of being classified in the autism category, and it showed that it increased by 1.21 per year, so there was an increasing probability of being classified in the autism category each year during that particular interval.

SPECIAL MASTER HASTINGS: Let me just add

that you're on Slide 12 now, correct?

THE WITNESS: Sorry. Yes.

SPECIAL MASTER HASTINGS: Go ahead.

THE WITNESS: Slide 12, yes. In the meantime, nationwide there was also a decreased likelihood for children to be classified in the learning disability category and in the mental retardation category. These are significant declines. The odds ratios are close to one, but they are significantly showing a lower likelihood to be classified in this category.

So the next step was for him to say these are trends across the U.S., but let's see within each state if there is a direct relationship between the tendency for an increasing prevalence of autism and a tendency for a decreasing prevalence of learning disabilities and mental retardation, and in fact he found that in most states there was this relation between a trend up for autism and a trend down for LD and MR, showing that the two trends were actually associated.

Then the third analysis he did was to postulate that if he was right or if the hypothesis would be diagnostic switching we should see that in the trajectories a historical trend in mental

retardation and in learning disability. There should be a deflection downward at the time where the autism category was created in 1993-1994.

He tested inflections down in the trends of learning disabilities and mental retardation, and in fact there was a significant downward trend appearing in 1994 and for LD actually another trend in 1999 as well, so showing that there was really in terms of the relationship in time a close correspondence between the two trends.

Then finally he conducted an analysis looking at not only autism, but equally other kinds of special categories which are recognized in the Department of Education data. There are other categories, other health impairments, which usually include ADHD in particular; trauma brain injury, which was a category which was created in 1997 if I'm correct; and developmental delay. All of them together showed upward trend in most states, so there was all this group of conditions that were showing in most states except Pennsylvania.

He quantified this trend, and it was about 12 per 1,000 for the increase. If I could go back? And then he looked at the decrease for mental retardation combined with learning disability and

found that the decrease was about 11 per 1,000, and it seems that the two trends do cancel each other out.

So the next slide, which is Slide 13, relies on this same study and shows graphically that -- can I have a pointer maybe? Thank you.

MS. RICCIARDELLA: I don't think it's working.

THE WITNESS: I'll pass. The upper line is following disability, and you see that there is a trend, and then in 1994 it starts to plateau and go down. In 1999 there is a decline in that trend. For the mental retardation, which are the triangles, again in 1994 there is the onset of a slight downward trend, which is consumed in the subsequent years.

In parallel, you see the black line is for the increasing number of children with autism, and the circles identify the combination of autism, other health impairments, trauma brain injury and developmental delay.

This combination of categories shows actually the steepest increase over this period of time, showing, by the way, that the increase in the number of children with autism in the Department of Education data is not specific to autism. It has been documented in other studies that other conditions,

particularly other health impairments which include many children with ADHD, have also increased over the years.

So the conclusion of this particular set of analyses, which I think is very important for the U.S. debate, shows on this side that he really concluded that the data do not support a claim of an autism epidemic because in these prevalence figures most data are well below epidemiological estimates, and then he showed that there is evidence, strong evidence, for diagnostic switching or diagnostic substitution over the last 10 or 15 years.

BY MS. RICCIARDELLA:

Q I want to discuss now studies that have been done that specifically looked at whether the MMR vaccine may be casually associated with autism spectrum disorder.

Before we get into that though, when was the purported causal association between MMR vaccine and autism first hypothesized?

A That was hypothesized in 1998. At the time I was in the U.K., as you know, as a autism clinical and research person. I would say that I and my colleagues were all surprised that this hypothesis would be put forward because a lot had been done in

the research on the causes of autism. Measles infections were never really looked at as a potential cause, and that came as a strong surprise.

As I was in the U.K. at the time, I was involved in the review of Dr. Wakefield's research immediately. There was a special panel which was convened by the Medical Research Council. We reviewed in his presence and the presence of his team his initial findings, and following this particular claim some of us, including myself, were engaging in research to test aspects of empirically the predictions which followed from his claims.

Q And the epidemiologic studies that we're about to discuss today were also designed to test that hypothesis as well?

A Yes. One of the first ones was led by Taylor in the United Kingdom. Maybe we should have the next slide.

Q Before we get to that I'd like to talk about the three categories of studies, of epidemiologic studies that have been done to test this hypothesis.

A Yes. Oh, yes.

Q You referred to Slide 14?

A Yes. That's Slide 14. Yes. Basically a review of this epidemiology can be done around three

things.

The first question, which is addressed by a combination of cohort studies and case-control studies, are really epidemiological studies where one looks at individual children who were exposed to the vaccination, and we want to assess if exposure to MMR increased the risk of autism using different designs. That's the first set of questions.

Then the second set of studies which we'll review are what would be described as ecological studies where here you don't look at individual children, but look at rates of autism in particular populations over time, and you try to assess if change in the immunization policies or, for instance, the introduction of MMR or the discontinuation of MMR, if there was a relationship between the two, we should see that these changes in immunization policies should affect the rate of autism.

Then the third set of studies have tried really to validate the Wakefield ASD-GI, as was said the other day, or the autistic enterocolitis phenotype, and I will speak to that later.

Q Let's look at the studies that address the first question about whether individual exposure to MMR increases the risk of autistic spectrum disorder.

You referred a moment ago to a study done by Taylor, et al. that was published in 1999 in the *Lancet*.

A Yes.

Q And I'm referring to Respondent's Exhibit P at Tab 145. That study was done in the United Kingdom, correct?

A Yes. It's a landmark study because it was published a year later. It was well done, very well evaluated by various committees. The epidemiological analysis is very sound. Actually they use different techniques so there are ecological analysis but also cohort analysis, so it's a complex study in terms of the design and the analysis.

What is important to know for the U.K-based study is that MMR was introduced in 1988, so actually children who were born in 1987 started to be exposed to MMR, which was introduced I think in October or June 1988, so that provides a contrast to the period which precedes it free of MMR and what follows is MMR exposed.

Now, in that study, they identified children who have an autism diagnosis either what they call core autism or atypical autism, which is like PDD-NOS, in eight districts in the North Thames region in London, and they looked as well at special educational

registers, so they identified cases like that.

They abstracted the data from the records. They looked at parental concerns, first parental concerns, age at diagnosis, regression or no regression. They also looked at the GI symptoms at a later stage, confirmed the diagnosis in a number of records, and in that analysis they portrayed the trends over time in rate of autism.

You could see, as we have seen elsewhere, that there is a smooth increase in the number of children earning such a diagnosis over time, so what they did is they modeled the long-term trend which signaled this change in probably diagnostic practices and identification.

Then the clinical analysis that they did was to look at whether or not after the introduction of MMR in 1988 there was a step up. If there was an effect of MMR in the rates of autism there should be a long-term trend, and then after the MMR there should be a step up in the trend. You can see visually those, so mathematically using personal regression as they did that there was no effect of the MMR introduction in 1988.

They also restricted their analysis in years which were post 1987, so these were years where

children were exposed to MMR, and they looked at vaccine coverage with MMR and the rates of autism in years from 1987 to 1992, and then again they failed to identify that there was any relationship between how much autism was there and how much MMR coverage there was during this particular period of time.

They also did some other analysis which were looking at age at diagnosis, so they actually split up their sample of autistic children in those which were post 1987, and then there were children who were never exposed to MMR, there were children who were exposed to MMR after the parents were already concerned, and there were a large group of children who were exposed to it before any parental concerns, so these three groups were different in terms of exposure, and the relationship between MMR immunization and onset of first parental concern, and they looked at the age of diagnosis in these three groups.

If there was a relationship between MMR immunization and the onset at least in the third group of parental concern shortly after the MMR we should see that the age of diagnosis in the group which had MMR followed by parental concern should be different from the other two.

They didn't find any difference. There was

no difference at all in the patterns of diagnosis, in the age of diagnosis in these three groups, showing that MMR immunization had nothing to do with that particular outcome.

Then if I can have the next slide, which is Slide 16? This study is a particular analysis which is called a case study, and the question which is addressed here, they tried to look at postvaccination clustering of particular events, so they looked at is there a tendency of the diagnosis to be clustering shortly after the MMR vaccination? Is there a tendency for parental concern to cluster after immunization? The same for regression.

All of the analyses were negative. There was no evidence that there was a clustering in time following MMR vaccination of any of these behaviors or indices of the autism onset.

There was one exception with the parental concern which was that, as you see on that slide, there was parental concern in the sixth month which followed MMR immunization. The rate of incidence is 1.48 and is significant, but when they looked actually at the data in the U.K. children receive their MMR at 13 months of age, and in that particular data set a lot of parents become concerned at age 18 months.

So there was actually a built-in correlation between age of MMR and age of parental concern because a large number of parents were reporting the first onset at 18 months, but the 18 months is due to record bias. They are showing that a lot of people don't know exactly when they became concerned specifically. They say either 24 months of age or 18 months of age. It speaks of their recognition at particular ages like that. So that's why the explanation, and they showed it in other analyses.

So basically the idea is that there was no evidence of a clustering of onset of autism, onset of recognition or diagnosis shortly after MMR or at different time points or time intervals following the MMR immunization.

Q Now your report also references a study done here in the United States by DeStefano, et al. that was published in the *Journal of Pediatrics* in 2004. I'm referring to Respondent's Exhibit P at Tab 38.

Now this was a case-control study looking at autistic spectrum disorder children in metropolitan Atlanta. Is that correct?

A Yes. It's a case-control study where they looked at and identified 900 cases in the region of Atlanta. Actually, they had the immunization records

through school records only in 660 I think subjects, and they matched about three controls for each case so they had about 600 cases and about 1,800 controls. About.

The first graph shows the idea was that they looked at the time of immunization, the age of immunization in the two groups. Again, the assumption was that if there was a relationship between MMR immunization and the diagnosis the cases of autism should be more often vaccinated around 18 months of age or around two years of age, which are the times at which autistic symptoms become the most obvious.

As you can see, the repetition of dates of MMR immunization in cases and controls are actually remarkably similar. About two-thirds of the cases and controls received their MMR immunizations between 12 and 17 months of age, showing that there is no particular again clustering of MMR immunization dates in the cases compared to the controls.

They also conducted other analyses where they looked at the effect of MMR age in subgroups, including regression or not regression, mental retardation or not, and they could also in the subsample conduct more advanced analyses adjusting with multiple factors which they could access through

birth registries over Georgia.

All the analyses were basically negative. There was a bit of a difference at three years of age for children with autism who tended to have more vaccinations of MMR by age three, but that was interpreted as reflecting the fact that the child who has a diagnosis at age three and enters a publicly funded intervention program, there is a requirement that you will be vaccinated.

So at that late age, which is three years of age, there was a slight increase in the number of MMR vaccinations in the case group, but that was reflecting this particular constraint of accessing services at that age.

Q There's another study of this that answers Question No. 1 out of Denmark, and that's Madsen, et al. published in the *New England Journal of Medicine* in 2002, and I'm referring to Respondent's Exhibit P at Tab 105.

Doctor, this is a retrospective cohort study of all children born in Denmark from January 1991 through December 1998, correct?

A Yes. That's on Slide 18. Now, this was a very important study because of its location, which is Denmark, and they use statistical power.

Just to recap, in Denmark people are born with a unique identifier, and it allows researchers to interface the database. They have a National Psychiatric Register where all psychiatric diagnoses are recorded, including autism, and they have also an immunization database so they could basically reconstruct, retrospectively create a cohort study.

The design is very simple. It's to look at children who were born between 1991 and 1998, and that covers in that study half a million children in that study, so it's really powerful. Then you follow children between the age of one up to the point where there is either death or the end of the followup period or a diagnosis of autism so you can really reflect. You go after them.

You follow up children over time, and you know if they have been exposed to MMR or not exposed to MMR because you have the immunization data and they are very precise. It is designed particularly as a cohort study, so you can calculate in the group of unexposed children to MMR the incidence of autism or ASD, and you can calculate the incidence in the group who have been exposed to MMR, which was larger in that study. There were 82 percent I think of the children nationally who were immunized with MMR.

The ratio between these two incidence rates in both groups is an indication of the relative risk, and you can see on that slide, and this is after adjusting for various concerning factors, the relative risk is 0.92 for autism when adjusted for particular concerns, and it's .83 for the group with ASD. I think they had 787 cases of ASD.

So again a very well powered study in which both relative risk for autism and the global ASD are not significant. The confidence interval includes one, and in fact the estimates are below one, suggesting that it would be not even close to showing any type of association.

So it was a very powerful study because of its design, which is a cohort study, the national representativeness of the cases and the huge number of cases and extreme statistical power.

Q Now, you did a study or you participated in a study that's known as Smeeth, et al. that was published in the *Lancet* in 2004, and I'm referring to Respondent's Exhibit P at Tab 137.

What was the objective of your study?

A In this study actually after the review of Dr. Wakefield's work with my colleagues of the London School of Hygiene and Topical Medicine -- they are

epidemiologists working in specifically in infectious disease -- we decided to see if we could test the Wakefield hypothesis this time using a case control study.

In the U.K. there is what is called a GPRD, which is a General Practice Research Database, which contains -- it varies, but sometimes contains up to 400 or 500 general practices across the country, and it covers several million people who were attending these GPs.

We selected cases which were born in 1973 or later so that they would have a chance to receive MMR at different ages. We selected 1,300 cases that we matched to 4,500 controls I think. The controls were carefully selected and matched by age, by gender. The control children were followed in the same general practice as the cases.

In that study we also obtained medical records and a subsample of several hundred. I think there were 200 or 300 cases. I rated them all to confirm the diagnosis and get some more information about their clinical characteristics, and there was evidence that the diagnoses were varied in that study.

Then we reconnected our analysis and in essence -- if we can have the next slide?

SPECIAL MASTER HASTINGS: Now we just moved from Slide 19 to Slide 20. Go ahead.

THE WITNESS: Yes. So these are the odds ratios. The odds ratios are estimates of the relative risk in a case controlled study.

You can see that for autism if one looks only at the column which is Adjusted Odds Ratio, which is what matters, we have an odds ratio of .88 for autism, which is again much below one, not significantly different from one, which would indicate a protective effect overall, but it's no different from one, but below one and not significant therefore.

For other PDDs it's the same, 0.75, again suggestive of no association between autism or PDD and past exposure to MMR.

We've conducted multiple analyses and subsamples, for instance, because we were concerned that some confounding could have occurred due to the fact that some children were born and influenced by the media campaign after the Wakefield hypothesis was released.

We restricted our analysis to children born before that, and therefore the parents or the GPs would not be affected by that. Again, that is the reason we had do so there is a range of different

analyses, and the study is very well powered again because we have a sample size, a combined number which is almost 6,000, which is extremely powerful.

So our study was negative. It was a study funded by the MRC. The next slide I would like to show that in this study --

MS. RICCIARDELLA: Slide 21.

THE WITNESS: Yes. This is Slide 21. We had done our own study that you can see as being indicated as present, but we tried to do a kind of meta-analysis, which is trying to look at other studies which have estimated relative risk as well, and the Madsen study provided two relative risks that we could really use. The DeStefano study also provided such data.

We had other data, but we could not use it for technical reasons, so this slide shows in the blue or greenish boxes the location of the relative risk estimate in each study. You can see the line which is the vertical line which says 1) Effect. That's the line of the null hypothesis where there is no effect, no association.

If any study had given a hint that there would be some association, we should have odds ratios or relative risks which would be on the right-hand

side of these vertical lines. There would be an increased risk of 1.5 or two, and you can see none of these studies show that.

The four independent studies show relative risk estimates which are in the same kind of range. There is no heterogeneity of estimates across the range, which allowed us to pull them together and generate a combined pooled estimate for relative risk, which is the combined figure which you see at the bottom.

The actual value of this pool estimate is 0.87. It's not significantly different from one, but again it's the value which is attached to the association between MMR, again which shows in effect no association across for the different study.

BY MS. RICCIARDELLA:

Q The last case control study I'd like to discuss that answers the first question that we put forward is the DeWilde study published in the *British Journal of General Practice* in 2001, and I'm referring to Respondent's Exhibit P at Tab 40.

Doctor, the hypothesis of this study was that if MMR vaccination is related to behavioral decline in children who are subsequently diagnosed as autistic then such a behavioral decline would be

reflected in increased consultations with that child's doctor.

What were the conclusions though of this DeWilde study?

A Yes. I think it's important also to realize that in the U.K. there is a universal national health service which is free for all, so everybody has access to GPs registered in the GP practice, and there is no fee to access the doctors in principle and is universal, so it's a system in which doing these studies can be informative.

Again, the prediction is that if there is a massive change following MMR of course you would expect that to be in days, 60 days or six months. Following the MMR immunization there should be onset of symptoms, and therefore this would translate into parents bringing their child to the GPs to express their concerns.

That's what they did. They looked in another electronic database called the Doctors Indefinite Network, and they had children who ultimately were diagnosed with autism, 71. They matched them to four controls per case, so 280 controls.

They had the MMR immunization base, and they

created an interval of two months before and after the MMR or six months before and after MMR, and they calculated for each group how many consultations there had been, and they compared the difference in the number of consultations in each group. The expectation would be that there would be more consultation in the autism group following MMR immunization.

In fact, as you can see in the pairs of different case control coloring the mean is not different. There is not a difference of the mean, of the paired means between the two groups, and they are no different from zero. There is no effect whatsoever.

What is interesting is that when they did the same thing, but looking this time at the number of consultations preceding the diagnosis of autism 60 days or 180 days before, then they could document that in the autism group there was an increased number of contacts between parents and GPs shortly before the diagnosis was made, again suggesting that this analysis or their report was actually sensitive to what they wanted to show.

In short, this does not support that there would be a dramatic change in a child which would lead

to GP consultation following MMR, and in fact as I recall now in this case group there were 71 cases. Only one case out of the 71 was diagnosed with autism within six months after the MMR immunization.

Q And we've been referring to Slide 22. Doctor, I'd like to look at the second type of study design that we discussed earlier that looks at whether rate of ASDs has been affected by MMR vaccination policies.

I'd like to refer to a study that you did in 2004 that was published in the *Journal of Psychological Medicine*, and I'm referring to -- I don't have that page.

A Yes. This is a study that we've done in the U.K. where we secured the membership of the National Autistic Society, which is a well attended society in the U.K., and we had 2,400 births of autistic subjects between 1959 to 1993.

Then we used the comparison group, which was made up of 4,600 Down's syndrome controls, because we wanted to test. If we were to find anything, we wanted to see if it was specific to autism or not.

We also got data on infection or outbreaks of measles because the U.K. of course, as most countries, records the number of measles

notifications. Especially at the time it was a very active monitoring system, so we could get this data which were on public record.

If we can have the next slide?

SPECIAL MASTER HASTINGS: We're going from Slide 24 to Slide 25 now. Go ahead.

THE WITNESS: Sorry. The period spans 1959 through 1993, and if one looks at the vaccine event it's important to know that between 1959 to 1967 there was no vaccination at all against measles. At that time it was just a wild measles epidemic.

Then in 1968 there was the introduction for the first time of a monovalent measles vaccine, and then in 1987 or 1988 for children born in 1987, MMR was introduced, and the last column is there was a change in the mumps component of the MMR vaccine, which is slightly irrelevant to this presentation.

We could therefore construct intervals to look at a particular event occurring at different time points, and we modeled the data using four week intervals looking at prenatal exposures and postnatal exposures up to the age of 18 months.

We did a set of analyses, but I will summarize them in the next slide. Here in this slide the first analysis we did was to look at the possible

relationship between wild measles outbreaks or epidemics occurring between 1966 and 1986, so before the MMR was introduced, just to see if we could document any association between measles outbreaks or epidemics and rates of autistic births.

The reason for that is measles epidemics have actually a biannual cycle. It goes one year you have a peak of incidence and then it goes down the next year. Usually it fluctuates, so because of its fluctuation in the incidence of measles you would predict if there is a connection between autism that birth of autistic subjects would be related to that. We did establish there was no relationship as would have been parroted from past studies.

Then the second set of studies that we did was to look at the effect on the times of autistic births over this long period of time of introducing different vaccines. When the monovalent measles vaccine was introduced in 1968 there was absolutely no effect on the underlying trend for autistic births.

Then in 1988 this was the date where MMR was introduced, and we hypothesized that if there was an effect of MMR we should have again a step up in the trend in autistic births. What we found is in fact no effect. Yes. No effect.

No. No. There should be another. It has gone. I think it has gone from the slide. Anyway, if you look at the paper you will see that the trend continues, and there is no step up which is predicted if there was an association. It has disappeared from PowerPoint manipulation.

MS. RICCIARDELLA: Technical difficulties.

THE WITNESS: The graph is in the paper in my references. Okay. So let's move on.

BY MS. RICCIARDELLA:

Q All right. Moving on, your findings have been shown in other studies as well, for instance, a study by Dales, et al. that was published in *JAMA* in 2001. I'm referring to Exhibit P at Tab 33.

A Yes. This is another ecological study which was done in the U.S. The data actually originates from California. It does compare young children diagnosed with autism in the developmental centers of California, and you see the trend is from 1980 to 1994.

In the green you have the number of children diagnosed with autism. These authors secured data from California to look at the proportion of 17 months old or two years old in California which were vaccinated correctly with MMR. So here you have in

red the proportion of children vaccinated with MMR by age two over time.

This estimate is obtained regularly by surveys which are conducted in kindergarten schools, both private and public, across the state of California. The usual sample size that they use is 600 to 2,000, so it provides an estimate for coverage and a trend that you can use.

You can see that if you just put a percent increase on this graph there is a 370 percent increase in the number of children diagnosed with autism from the start or the beginning of the study period and the transfer of MMR coverage at two years old is only increasing slightly by 14 percent. So again, the disconnect between these two trends suggests no relationship between the two phenomena. And that has been shown as well in other studies.

So this is Slide 28.

Q And, Doctor, this is a case study that was published in the *British Medical Journal* in 2001 that's found at Respondent's Exhibit P at Tab 95.

What did this study consider?

A It's again using the GPRD data and a sample size which is I think a few hundred. This analysis is probably based on more like 100 cases.

They showed again that the risk of autism in I think boys which were up to age five increases from a low point in 1988 up to the highest point in 1993, but at the same time the green line at the top indicates that the uptake of MMR is quite steady during that same period, so there is no change in the coverage by MMR during that period.

Actually the MMR coverage here, just for historical note, is 97 percent. That was before Dr. Wakefield's publication. That was during the efficacy of the vaccination policy in the U.K. during those years. Again, the disconnect between the two curves suggests that there is no relationship between the two phenomena.

Q Now, Doctor, you published a study recently last year in the *Journal of Pediatrics*, and I'm referring to Respondent's P at Tab 74.

A Yes.

Q And you looked at developmental disorders in Montreal, Quebec, Canada. What did this study consider?

A This is Slide 29, and just the design of this study was to look at we surveyed children in a school board which has about 27,000 pupils registered between kindergarten and grade 11, and this is a

school board which is located in the west part of the island of Montreal with which my department has a particular relationship.

We identified 180 children who had a code of autism in that school board. We also obtained some immunization data from different sources -- the Health of Ministry -- and to estimate MMR uptake we relied on a survey done in Quebec by a public health department which over the years has done repeated surveys of two- or three-year-olds which allowed us to estimate a trend for MMR uptake during the study period.

So what we found, and this is the next slide, is this is first portraying the rate of autism in each successive birth cohort. You can see the children who are born between 1987 on the left up to 1998 on the right. The survey was done in 2003, so children were age five to 17.

For each birth cohort we have a prevalence rate which is specific to the birth cohort, and you can see that when we model the data here there is no exponentiation. It's a linear increase. The best line, the best fitting model, is a linear model where you have on average a 10 percent increase in the diagnosis of ASDs per year over a successive birth cohort.

So that's what we tried to explain. Having that trend, the question is can we relate that trend or is this trend affected by something happening in the immunization schedule. We looked at the MMR coverage and the data, which are those ones you see in pink, and basically the MMR coverage at the beginning of the period is about 95, 96 percent, and at the end of the period it drops to about 92 percent on average.

This is a small decrease, but it's significant if you do a statistical test. Again, as you see the decline in MMR coverage and the constant increase by 10 percent each year of the rate of the disease, you can see that there is no relationship between the two. When you do modeling of this data you don't have any kind of relationship.

We had also the opportunity in that study to look at another hypothesis which has not been tested thus far, which is shown on Slide 31. This was because in most countries MMR is given twice. For instance, in the U.K. the policy is to vaccinate with MMR between 12 months and 15 months of age, usually around 13 months of age, and then to give a booster when the child goes to kindergarten at age five. In Denmark it's 15 months and 12 years of age. Each country has its own policy for reasons that I don't

understand.

In Quebec there was one MMR dosing schedule up to 1995 and then they decided to increase the vaccination coverage and to introduce from 1996 onward a second MMR dose, so the first MMR dose was given at 12 months of age, and the second MMR dose, which was given after 1996, is given at 18 months of age.

So then we had an opportunity to look if a two MMR dosing schedule was increasing the risk of autism or affecting the risk of autism. So what we did, we looked at the first 10 years or so of the study where we had this smooth increase in ASD rates and a regimen where there was just one MMR dosing schedule.

So we decided if the trend continues we should predict to have these kind of rates if the trend continues. If the introduction of the second MMR though increases the risk, we should see again a step up in our trends.

What we observed in the subsequent years when there were two MMR doses was actually something which was no different from the prediction under the one MMR dosing, so that showed that the introduction of the second MMR dose at 18 months of age does not affect the rate of autism.

Q Now, there's a study that's been done that actually looks at autism rates after MMR had been taken off of the official vaccination schedule, and I'm referring to the Honda study out of Japan that was published in 2005 in the *Journal of Child Psychology and Psychiatry*, and I'm referring to Respondent's Exhibit P at Tab 87.

In Japan, MMR was taken off the official vaccination schedule in 1993. Is that correct?

A Yes. This is shown in Slide 32. Ecological studies can be actually quite informative and powerful when you have situations in the length of exposure which allow you to test really if a change in the level of exposure in a population affects the rate.

So when you have two correlations where you go up or down in its introduction the interpretation can be spurious and difficult, but when you have a situation when you have suddenly the discontinuation of an exposure then you can really test by looking at what's happening before and after if there is a relationship or not.

In Japan what happened is that they introduced MMR I think in 1988, and soon after the introduction of this vaccination they found out that an unusual number of children developed aseptic

meningitis due to the mumps strain in this MMR vaccination. They were using the URB strain, which was sort of a bad strain.

It was soon recognized as a problem, and as a result of that they actually advised to discontinue the use of MMR in Japanese children, and then they reversed it in 1992 to the use of monovalent measles vaccine. So what we see here is from 1988 through 1992 you see the decline in the use of the MMR vaccine in Japan, and then in 1992 it stops altogether.

The other lines on the graph show the rates of autism spectrum disorder in prefecture named Yokohama, and you can see that when the MMR vaccination uptake is declining it has no effect on the rates of autism, which are either steady, if you look at the study, or steadily increasing, and when MMR is completely discontinued there is no evidence that it has an impact on the rate of autism.

In fact, the rate of ASDs continue to increase after the total discontinuation of MMR, including the rate of regressive autism, again showing that discontinuation of MMR does not lead to a decrease in the frequency of regressive autism.

Q Now, the third area of epidemiologic study that you mentioned earlier has looked at the proposed

MMR/autism hypothesis, but focusing specifically on whether there's this new phenotype of autistic enterocolitis.

Doctor, you were asked to present information before the Institute of Medicine in 2001 about this postulated new phenotype, were you not?

A Yes.

Q What did you tell them?

A Yes. At the time I was in England, but I had really wanted to test to see if there was some validity in the clinical phenotype that was described by Wakefield.

SPECIAL MASTER HASTINGS: Now we're on Slide 34. Go ahead, Doctor.

THE WITNESS: Slide 34. It's important to look at sort of not the history, but, as we described earlier, there are some autistic syndromes which we know arise through particular causes, and particular medical conditions can give rise to autistic syndromes.

When it is the case, these children who have autistic disorder and Fragile X or autistic disorder and a particular condition, they have been well studied symptomatically and themalogically, and they usually have different clinical features or different

clinical correlates.

So, for instance, if we take Fragile X children meet criteria for autistic disorder, but their behavior is actually different. Fragile X boys in particular are known to have particular gaze avoidance, which is not what we see in autism. When they approach you and you say hello, they just turn their head up as if looking at people was hurting them. This social anxiety and this gaze avoidance is very typical of Fragile X with or without autism.

They also have unusual attention deficits. Hyperactivity levels are high. The mental retardation is extremely high in males, and they have also physical features. They have a dysmorphic syndrome which becomes more prominent during puberty or maturity but also can be seen in young boys.

So there is a set of physical and behavioral features which are characteristic of autism when it occurs, and the same for tuberous sclerosis and the same for congenital rubella. So it's very logical to assume that if there is an autistic or -- there should be a phenotype of these children which is different from the average autistic child.

I reviewed very carefully Dr. Wakefield's paper and his own presentation at the MRC in 1998. In

his original paper, there is actually very little data to go for to describe this phenotype. If one looks at the *Lancet* paper, the MRI findings were fine. There was no evidence of brain abnormalities. He actually tested the CSF of these children, and there was no abnormalities in the CSF. There were no neurological signs.

So the only really pieces of evidence that we could go for to validate for certain were three things. He said that there was normal development and then regression; that the regression occurred he said on average 6.3 days after the MMR shot, so there is a close time association between MMR and the onset of symptoms in the child, otherwise no more up to that point; and then there are GI symptoms at the same time which develop in that child. Of course, if you can do endoscopy you could see his LNH findings, but which are nonspecific as we know.

We could therefore try to test empirically whether or not the syndrome regression, early normal development, regression, regression days after the MMR associated with GI symptoms, has some validity. That's what we did and others did over the years.

BY MS. RICCIARDELLA:

Q Doctor, if MMR were causally linked to the

development of autism, particularly regressive autism, then one would think regression in autism is a relatively new phenomenon.

A Yes.

Q Is that the case?

A One prediction of Dr. Wakefield's original description would be that he believed initially that regression -- he had described regression in autism because he had no autism expert involved in the original study, and when he presented the findings he really believed that it was a new kind of a phenomenon.

In fact, it's not. Regression has been described in the autism literature for decades. You have here just one slide, but I could provide --

SPECIAL MASTER HASTINGS: And now we're on Slide 35, correct?

THE WITNESS: Yes, 35. I could provide quotes by multiple British scholars or even Kanner in 1943 described regression in some of his relevant cases.

You can see. Let's say, for instance, Case No. 8 began to speak at 10 months of age, but stopped at 14 months and lost contact with people. This is just one description amongst many of children who had

this regression, and I chose that reference because it's 1964. 1964 is an era when there was no measles immunization, so that's why I chose that one in particular.

We actually know something about the rate of regressive autism in old studies. Maybe if I could have the -- yes. This is a slide which gives some estimates of regression as part of autism, but in days when there was no measles immunization at all.

For instance, take the first study. This is the first ever epidemiological survey conducted in autism.

SPECIAL MASTER HASTINGS: And now we're on Slide 36. This will help us, Doctor, later on when we read the transcript. Sorry to keep interrupting.

THE WITNESS: I apologize. So this first study by Lotter in 1966 documents a setback in the development, which includes speech loss -- it's exactly what we call today regression or loss of skills -- in 31 percent of the children.

You can see other studies that have rates which are anywhere between 25 to 30 or 40 percent. It was defined in different ways in different studies, hence the variability in rate, but the phenomenon was there and not such a rare occurrence.

It's important to recall that today in the recent studies, regressive autism occurs in the best studies, the considered studies. Twenty percent of the children with autism or PDD-NOS have the sort of experience of a loss of skills in the second year of their life.

BY MS. RICCIARDELLA:

Q Have any studies directly tested whether regressive autism has increased over time?

A Yes. Besides comparing historical studies with recent studies, there have been direct testing as to whether or not the rate of regressive autism has increased over time. It has been done in different studies.

Q One such one is Taylor, et al. published in the *British Medical Journal* in 2002?

A Yes.

Q Just for the record, I'm referring to Respondent's Exhibit P at Tab 146.

What did this study investigate with regard to regression?

A This is Slide 37.

Q Very good.

A This is a study which I described before by Taylor, the first 1999 paper. This is a follow-up

study where they looked at I think it was a subsample of five house districts with a sample size of about 370. They documented the regression in these children.

Again, the key point here is that 1988 is the MMR introduction in the U.K., so the first analysis is to look at trends over time in regression. When they looked at that using methods which were multivaried analysis adjusting for various factors there was absolutely no evidence that there was an increase in the proportion of children who were having regressive autism over this period which spans 1979 to 1998.

There was no evidence that after 1988 or following 1988 there was again an increase in the proportion of regressive autism. In fact, interestingly, in that study they looked at bowel symptoms as well and found that there was no evidence of an increase over time as well. There was no increase after 1988 of bowel symptoms presentation as a part of autism.

There was an association between regression and bowel symptoms in their study, but no link with MMR introduction in 1988, so that's one study which looked at trends over time. That doesn't show or

suggest that regressive autism has become more common or has increased after MMR.

Q There's another study out of Japan that hypothesized the incidence of regressive autism should have increased following the introduction of MMR in Japan but then decreased when MMR was taken off the official vaccination schedule. And I'm referring to a study by Fujiyama et al. published in 2006 in the *Journal of Autism and Developmental Disorders* or *JADD*, and it's found at Respondent's Exhibit P at tab 149. What did they find? What were the results after that hypothesis?

A This is Slide 38, and again, they relied on sort of a quasi-experiment, which is that there was a phase where there was no MMR, then there was introduction of MMR, and then there was this confusion, then there was a -- in the design, because you can see, if there were, you should see the rates of regression which fluctuates according to which period you are investigating, and then the way it's presented is there would be a special paper.

The first table 5 shows at the pre-MMR rate, you have 34 percent of children who have regression, and then during the MMR period, the line above, 35.6 percent children have regression, and then the table 6

provides a rate for the post-MMR period, where the rate is 40 percent, so 34, 35.6, 40, this is the time sequence of the proportion of regressive autism pre-, during, post-MMR, shows no difference which would reach or even approach statistical significance.

Again, a nice design which shows absolutely no effect of MMR on the proportion of regressive autism.

Q Okay. Have any studies looked at inflammatory bowel conditions in relation to MMR and autism?

A Yes, the next type of hypothesis was to look at a possible association between autism and inflammatory bowel disorder. I mentioned that study the other day. I'll go quickly through it, but again, the idea was, when we reviewed Dr. Wakefield's results in 1998 with this MRC panel, multiple comments were made on the fact that in the previous 10 years, he had been publishing studies showing that there was an increased rate of Crohn's disease in the human population that he was trying to ascribe to the measles virus in several studies which were subsequently not replicated.

So there was this track record of claims and hypotheses that he still believed. So if he was right

in saying now that measles virus was not only increasing the risk of Crohn's disease and inflammatory bowel disorders, but also increasing the risk of autism, the prediction follows that in children with autism, we should find an increased incidence of Crohn's disease and inflammatory bowel disorders.

So that's what we tested immediately in 1998, because we had data which could allow us to do that, and in short, there is an English Maudsley Hospital series of children with PDDs, 762, psychiatric controls, 100 -- 8,000 or more, and then there is a French series of epidemiological data, 174 children with PDDs and almost 6,000 psychiatric and developmentally impaired controls.

So in those two data sets, medical disorders were recorded independently, and then you could look at what was the frequency of IBD, meaning inflammatory bowel disorders, which includes in that slide Crohn's disease and ulcerative colitis and other types of IBD.

As you can see, there was no case in both studies of IBD in the autism series, and there were a few cases in the controls because the controls were more numerous, showing that there was no association between autism and IBD.

And the prevalence of IBD in the two studies were actually quite consistent across the two data sets and consistent with what we know from literature, therefore suggesting that in both studies, there had been no systematic underestimation of IBD.

MS. RICCIARDELLA: And Dr. Fombonne has just been talking about the data presented on slide 40.

THE WITNESS: Yes.

BY MS. RICCIARDELLA:

Q Doctor, what does the autism research community know about the timing of onset of first symptoms of autism and its relationship to the MMR vaccination?

A On the previous slide, I just want to add that there have been other studies looking at IBD and autism. There is a study in the GPRD database by Black et al. in 2002 or 3 in the U.K., no association. A recent study by a large group of U.S.-funded investigators have looked at the same thing, comparing regressive autism versus nonregressive autism, and found no difference in the incidence of inflammatory bowel disorders.

So the other set of studies have looked at the idea of the timing between MMR immunizations and the onset of first symptoms, so that's what studies

have been done, and there are others which have done similar things. Let's assume that this is a distribution of the age at which parents recognize the first symptoms of onset. There is the spread, so that would be sort of parents who have a child who becomes autistic, and they would recognize the first problem at different ages. That would be at that slide actually.

Now it's easier under a situation where there is no immunization. Now there is an immunization policy which is let's give MMR to children at 13 or 14 months of age, and if the onset of symptoms develop days after the MMR, therefore, in populations where MMR has been used or children have been exposed to MMR, we should see that there is a shift in the age of onset of first autistic symptoms either in the whole population or in the subset of the population, and we should therefore have a bimodal distribution of age of onset in MMR-exposed children, or something that could be speaking to the close timing between MMR and onset of first symptoms.

So that's what we tested in a study which is now presented in slide 43 --

Q Doctor, before you talk about the study you published in 2001, I just wanted to make sure that the

record is clear that the Doctor was just talking about slides 41 and 42. And slide 43 refers to a study that he published in the *Journal of Pediatrics* in 2001. That's found at Respondent's Exhibit P at tab 60.

I'm sorry, Doctor. What was the purpose of this study that we are looking at at slide 43?

A The study was to compare the age at which parents first recognized symptoms of autism in different samples, two of them where the children had received an MMR immunization, on the right, and one of them which has not been exposed to MMR, and therefore, we wanted to see if there was any difference in the mean age of onset or mean age of parental recognitions in MMR-exposed children as opposed to unexposed children.

And you can see that the mean age of onset in the three samples, which were studied with the same diagnostic interviews by interviewers which were blind to the study hypothesis, that there is no difference, and we've looked at shapes of this parental disorder. There is no evidence of bimodal distribution in a subgroup at all, so again, showing that the timing is not affected by MMR immunization.

Then in the same study, we compared the unexposed and pre-MMR sample to the post-MMR sample

and calculated the proportion of subjects who had experienced some type of regression in their development, and again, the data were collected using the same standardized diagnostic measure, the ADI. And you can see that the proportion was 18 percent maybe in the first group, 16 percent in the second group, no difference between the two groups, and no suggestion that under an MMR regime or era, there would be an increased proportion of regressive autism.

Q And, Doctor, you've just been testifying about slide 44?

A Yes.

Q Okay. Now we're on slide 45. What does this slide depict?

A Slide 45 is, in the same study, we further conducted analysis to look at the possible association between regression and GI symptoms, because that's part of the postulated phenotype, so if there are some validity to the phenotype, we should see that GI symptoms are preferentially associated with regression, and in our study, but others have found slightly different results, we didn't find any association between GI symptoms and regression.

Q Doctor, has any study replicated your findings from your 2001 study?

A Yes. That's probably the next, and this is slide 46.

Q 46, exactly. And for the record too to be clear, Dr. Fombonne is going to be testifying about the Richler study published in 2006 in *JADD*, found at Respondent's Exhibit P at tab 124. Doctor, what did the Richler study conclude?

A Well, this study was actually set to replicate in a larger sample our initial findings in the U.K., and this study really gathered data from multisites of investigators which are really well established in autism research, and they added data on about 350 well characterized children with autism. About half of them had regressive autism and the other half nonregressive autism.

So they come out with a set of different analyses, but these are just two analyses which show, on the first, on the left-hand side, this is an analysis which looks at the age of MMR vaccination according to the presence or absence of regression, and the idea is that in that analysis, it's called a survival curve, so the proportion of unvaccinated children decreased as they got their vaccination over time.

So children are followed from birth to age

14 months, and as they age, in an increasing number receive the vaccination, and this is called a survival curve.

SPECIAL MASTER HASTINGS: What kind of curve?

THE WITNESS: Survival.

SPECIAL MASTER HASTINGS: Survival?

THE WITNESS: Survival curve.

SPECIAL MASTER HASTINGS: Survival of the fittest.

THE WITNESS: Yes, okay.

SPECIAL MASTER HASTINGS: Okay.

THE WITNESS: So in other words, if everybody is not vaccinated, you have a straight line at the top, and then if the line goes down, say that there is like 20 percent children are vaccinated, 40 percent, so those lines indicate the proportion in the sample who remain unvaccinated over time. So the idea is that if there is a relationship between MMR vaccination and regression, there should be different survival curves, and we should see that the regressive children do have a curve which goes down just after MMR vaccination, and that shows absolutely no difference between regressive and nonregressive autism in terms of the relationship with MMR vaccination.

And on the right, this is on children who have -- it's a harsher test of the hypothesis. They really looked there at those children who had an onset of first symptoms after the MMR vaccination, and then they broke down the sample into regression versus no regression. And again, when they did that, there is no evidence of the regressive subtype as an onset which is closer to the MMR vaccination than those without regressive subtypes who have an onset after MMR vaccination.

I hope it's clear, but it really gives us a very clear test of the hypothesis. And then on the line on the bottom you have, they put the hypothesis to an extreme harsh test. What they did is say, if there is any validity to this autistic enterocolitis theory, we should find children whose onset of symptoms is after MMR, whose onset is close to MMR, who regress, and who have GI symptoms.

So they selected in their database those children who have this profile: GI symptoms, onset after MMR and regression just after MMR. And they said, let's look at these children. They found 24 of them and they looked at their early development. And in all cases, they concluded that in fact these 24 children who were the best candidates for the

pediatric phenotype were in fact abnormal in their development before the regression and before the MMR vaccination, something that we spoke last week as well. So the study concluded that there is no evidence for this, no strong evidence for this Wakefield hypothesis and this phenotype.

BY MS. RICCIARDELLA:

Q Doctor, these epidemiological studies that we just discussed, answering the three questions, to a layperson are very technical, and I'll be the first to admit that maybe the specifics can get lost. What is the take-away from the epidemiological studies that have been conducted that have looked at the hypothesis of MMR vaccination causing or contributing to autism?

A Well, I think it's very clear that there has been now a range of controlled epidemiological studies which have employed different designs. We have cohort studies, which are quite powerful, we have case-control studies, we have ecological studies done in different countries, done by different groups of investigators, and all of them, if you look at all of them, they all provide data which are consistent with no association between MMR and autism, and I think the consistency of findings across studies, across countries, across investigators group, is quite

striking.

Q Doctor, in the United Kingdom, when the media first started reporting on this purported hypothesis of MMR autism, did that affect MMR vaccination rates in the U.K.?

A It did. It did. The coverage nationally I think was 96 percent in '97 for children with MMR, and then in 2003, as I recall, there was a publication in *Science* which showed that they had a decrease. The decrease was quite spectacular, and the national proportion was 81 percent. And this is again proportion which does not guarantee herited immunity and is usually associated with measles outbreaks and/or epidemics, and this is what happened in the U.K. And it has had a long-lasting effect, and it is sad.

Q I'd like to shift focus now. We were talking about epidemiologic studies that looked at the MMR autism hypothesis. Now I'd like to briefly discuss some of the studies that have been done that have looked at the possible causal association between thimerosal-containing vaccines and the development of autism. And we won't go through them all, but I would like to first ask you about a study done in Denmark by Hviid et al., published in *JAMA* in 2003, and I'm

referring to Respondent's Exhibit P at tab 88. What did that study look at?

A This is slide 47, and this is one slide to summarize again an important study which is originating from Denmark. Like the Madsen study presented before, this is a study which capitalizes on the fact that in Denmark, you have national psychiatric registers, an immunization database. You can interface them, you can have access to variables which allow you to some extent to control for confounding. And quite quickly, they could again construct a retrospective cohort study.

So the idea was to look at children, in that case, they looked at 460,000 children, again, a huge power, which were born between 1990 and 1996, and then they could then follow those who were exposed to thimerosal-containing vaccines and those who were unexposed to these vaccines. There was a change in vaccine composition in Denmark, so they had actually enough in each group.

And basically what they did is two sets of analysis. In the first batch, you get exposure in a categorical fashion, so they had a group who were not exposed to any thimerosal-containing vaccines and they could calculate the incidence of autism there, and a

group who received at least some thimerosal-containing vaccines.

So this is the first line, first the upper part of the table, and if you look at autism, the rate they show is 85. For other is this 1.12. None of them with significance close to 1, showing no increase in the risk of autism in subjects who have received at least some thimerosal-containing vaccine, compared to thimerosal-fee subjects.

Then they did a further set of analysis to look this time at the dose-response relationship, trying to see if maybe there could be some risk which would be carried on by only those with higher levels of exposure, so they broke down the sample by levels of exposure; no exposure, one dose, two dose, three dose. And then you can see that all the relative risks, they are all under 1 for autism and close to 1 for ASD, none of them is significant, showing that even at a higher dose, like the three dose subjects, there is no evidence of an increase in the risk of autism or ASD.

Again, the study is actually well powered, the national influence of this sample, no effect.

Q And Doctor, there is another study from Denmark by Madsen et al., published in *Pediatrics* in

2003, and I'm referring to Respondent's Exhibit P at tab 106. What did this study look at specifically?

A This is an ecological study which, again, looks at the effect of discontinuation of the use of thimerosal in vaccines. That occurred in 1992 in Denmark, for reasons which were completely independent of safety concerns. They changed the vaccine production parameters and didn't use thimerosal anymore after 1992. So again, we have an experiment of the nature where we have a period where vaccines contain thimerosal and then a period thereafter where there is no thimerosal-containing vaccine.

And what is clear from this graph is that the rates of autism are flat from 1970 to about 1989 or 1988, and then they start to increase, before, actually, the thimerosal is discontinued. Thimerosal doesn't change, there is no increase or no change in the thimerosal content of vaccines between 1988 and 1992, but the rates start to increase. And then what is more even striking is that when thimerosal is removed in 1992, there is no evidence that the rates are falling down or changing in their slope.

So that's again an ecological study which indicates a lack of a relationship between rates of autism and the amount of thimerosal exposure in the

population.

Q Now Doctor, you did a study that we've already discussed, the Montreal, Quebec study, and you looked at children born in Montreal between 1987 and 1998, and you also, with respect to thimerosal-containing vaccines, what did your study consider?

A Well, again, we had this opportunity to look at the relationship with thimerosal-containing vaccine, and we were actually fortunate that in the study interval where we had data on rates of autism in successive birth cohorts, there were actually changes in immunization policies and immunization production in Quebec. So that gives us a nice opportunity to look at whether or not this change in thimerosal-containing vaccines had an impact on the rate.

And there is a two source period when we've looked at the cumulative column on the right, a period where the total amount of ethyl mercury in that case is about 100 or 125 micrograms based on the official immunization schedule, which is outlined on the slide. And then in 1992, there is a change because no dose of HiB are introduced, and that led to several years, four years as I recall, where the vaccines contained up to 200 micrograms.

And then in 1996, the Quebec authorities

decided to combine five vaccines in one single vaccine shot. They included the polio vaccine with the DCT and the HiB, and because the polio is a live attenuated vaccine, it can not tolerate the use of thimerosal. It would actually denature the vaccine, so they had to remove thimerosal from the vaccine production for that reason. Nothing to do with safety concern, again.

So we have three years, 6, 7 and 8, in our study where there is no more use of thimerosal in the regular immunization schedule in Quebec. So that allowed us to, again, test, this is the rates of autism, they increased, as I said before, on average, about 10 percent for every subsequent birth cohort. It's a linear slope.

SPECIAL MASTER HASTINGS: Now you've moved to slide 50. Go ahead, Doctor.

THE WITNESS: And then on the right-hand side, the axis which is appearing gives you the amount of ethyl mercury contained in the vaccines of the -- assuming the child is entirely immunized. Then we have basically three kinds of periods, one period, initially, for five years, where they had let's say a medium level of exposure. Then we have four years of high level of exposure. Then we have three years

where the exposure is nil.

And then, I mean, just looking, if you visually inspect this data, you can gauge that there is absolutely no relationship between the underlying trend in rates of ASD which is going up with no change, whereas there are massive change in the thimerosal exposure due to this change in immunization production. So when we model mathematically these data and try to use the rates as different variables and look at whether or not the amount of thimerosal for each year predicts the rates, there is absolutely no statistical position which can be made.

And we did further analysis to restrict our data to children who have a narrow diagnostic autistic disorder. Again, same story. We also restricted the analysis to the subsample of children who were born in Quebec and therefore more likely to have adhered to the immunization schedule, and again, there was no change. But then that, like the other study, it shows clearly, visually, that there is no relationship between the two.

BY MS. RICCIARDELLA:

Q Doctor, have other studies been done that have looked at the purported causal relationship between thimerosal-containing vaccines and autism?

A Yes.

Q Can we bring slide 51 that just lists a few of the others?

A These are five studies here which are summarized on this slide. Verstraeten, Andrews, are two cohort studies, one in the U.K., one in the U.S. Heron is a study which is a cohort study from the Avon, an entrepreneur study in the U.K. It didn't look exactly at autism as an outcome, but there is a special educational category which contains autistic children and should have gone up if there was an association, and there was none. That's why I put it there.

There is a case-control study in the U.K. in the GPRD database, and there is another ecological study by Stehr-Green which applies to Swedish data, where they discontinued thimerosal, I think, in 1994, I may be wrong by one year. And again, all these studies showed no association.

Q Now Doctor, finally, on this issue, various scientific committees in the United States and in Europe have considered the evidence of a purported causal association between MMR vaccine and thimerosal-containing vaccines and the development of autistic spectrum disorders. What have those committees all

concluded?

A This is slide 52, final. And yes, multiple professional scientific committees have reviewed the various hypotheses deriving from the MMR postulated link with autism, or the idea that thimerosal and ethyl mercury would be associated with an increased risk of autism. I cite here in this slide just the American Academy of Pediatrics, the Institute of Medicine report in 2004, the U.K. Medical Research Council, who are just among the most prestigious scientific bodies which have looked at this particular issue, but there are multiple reviews published by different scholars worldwide in multiple committees in WHO, the European medicine agencies, there is a Canadian vaccine safety committee.

So all the committees which have reviewed these two hypotheses have all consistently said that there is no data to support this hypothesis. And in fact, the Institute of Medicine in 2001 had conducted the first review of these two questions and reached a very conservative conclusion and said, well, there is no evidence to support this hypothesis, but maybe we should have more research to evaluate then.

And in 2004, the committee of the Institute of Medicine just reviewed the new evidence which had

been generated in the last three years, and then their conclusion was strikingly different insofar as they decided that in fact the evidence was now quite consistent, coming from different groups, different study designs, different countries, showing no link between MMR or TCVs and autism, and they actually concluded that the evidence was favoring the rejection of these two hypotheses.

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

SPECIAL MASTER HASTINGS: Let's take our 15-minute break at this point. Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We are back from our morning break, and Dr. Fombonne is back on the witness stand, and we have Mr. Powers, who's going to be doing cross-examination on behalf of the Petitioners. Go ahead, sir.

MR. POWERS: Thank you, Special Masters.

CROSS-EXAMINATION

BY MR. POWERS:

Q Good morning, Dr. Fombonne.

A Good morning.

Q Although I think we've seen each other in the courtroom for the last week or so, we haven't

formally introduced ourselves. My name is Tom Powers, and as Special Master Hastings said, I'll be doing the cross-examination today on behalf of the Petitioners' Steering Committee and the Cedillo family. I noticed you were adjusting the microphone. Are you ready to go?

A I think so, yes.

Q Okay. Well, I want to start off by talking a little bit about some of the issues related to epidemiology and how epidemiology may or may not capture the phenomenon that we are looking at, and the phenomenon we are looking at, to make sure I understand your testimony, is autism within populations. Is that correct?

A No, my testimony had to do with epidemiological studies of autism, in general, in populations, had to do with the causation of autism as is examined in various epidemiological studies. It had also to deal with a specific of Michelle Cedillo's case, using both my academic knowledge, but also my clinical background and experience.

Q Exactly. Now, when we talk about autism, one of the first slides that you showed earlier today talked about epidemiology looking at diseases, and if I recall correctly earlier testimony that you gave in

this case, autism isn't exactly a disease. It's a syndrome. Do you remember describing it that way?

A Yes, correct.

Q So it's a little different than what one might typically look at when one is looking at a disease, because as a syndrome, it's a collection of symptoms. Is that a fair statement?

A Yes, autism is defined as a constellation of behaviors, so it's a disorder in that sense, but it can be measured with a high degree of reliability and the validity of the disorder has been well established.

Q Right, and I'm not talking about reliability or validity. I just want to make sure we are talking about the same phenomenon that we are addressing with the epidemiology, so autism, as examined by epidemiology, is a collection of symptoms, and that collection of symptoms has a diagnostic method applied to it, is that correct?

A Yes, that's correct.

Q And if I also recall from your first day of testimony, there are three main domains, and I want to make sure I'm making the right term, three main domains of symptoms, and within each domain there are approximately 10 different symptoms that your slides

mention. Is that a fair summary of what those slides said?

A Yes. I mean, there could have been more symptoms than 10, but just it's just the easiest way to how we operationalize the deficits indicated in the domain, yes.

Q And you actually anticipated my next question, which was, these total of 30 symptoms, 10 per each of the three domains that you listed, are those the only symptoms that are looked at to diagnose the autistic syndrome?

A No. No, no, the --

Q How many more are there?

A I don't know. I didn't even count if there were 10 on each slide. No, the symptoms could be probably multiplied by, I don't know, you could have like 20 or 25 indicators of deficits in each of the domains. I'm throwing that number very arbitrarily, so I don't know how many symptoms there are, but there are multiple symptoms which can relate to the same underlying deficit.

And in the *DSM-IV* diagnostic system, in fact, you have the diagnostic criteria, there are only 12 diagnostic criteria in *DSM-IV*, and these are more there for symptom groupings if you wish.

Q Yes. And then in addition to the symptoms, you have ranges of severity for each of those symptoms too, is that correct?

A Yes.

Q So within a population of people who have been diagnosed with autism, I mean, if you start doing the computational math and started multiplying the number of possible symptoms that might occur, you could have potentially autistic people, hundreds of autistic people, all diagnosed with autism, but each with a different collection of symptoms and a different range of symptoms. Is that fair?

A Yes, it's fair.

Q A very, very complex symptomatic disorder, is that fair to say?

A Yes. I'm not sure it's more complex than any other medical entity. If you take any neurological disease which is well-characterized, take tuberous sclerosis, for instance, the phenotypic presentations will be as variable than autism.

Q Right. And believe me, I am not going to stand up here today and try to introduce more complexity by talking about additional complex disorders. I think the complexity that we are talking about here with the symptom presentation is something

that bears a little discussion, and that's all I want to focus on. It's not to compare it to the complexity of other disorders or diseases.

And I also understand your testimony to have been that autism doesn't have a, in your mind, a bio marker. There's no clinical test that you can do, no pathological test that you can do, to determine if somebody has autism. It's entirely behavioral, defined by the symptoms that you've already talked about, is that right?

A Yes, no, there are some biological markers of autism but they are not sensitive enough or specific enough to be helping us in the diagnostic process, so as a result, the diagnostic process rely on a developmental and behavioral evaluation of the kind that we discussed.

Q And it's an evaluation that has evolved, as you were talking about today, over time. There have been different diagnostic criteria as well as different diagnostic methods applied over time, is that correct?

A Yes.

Q And the overall result of the application of those methods, if I'm summing up your testimony, would be that the methodology by which one examines the

autism disorder in populations has led to higher numbers of prevalence, is that correct?

A The methodology of?

Q Of diagnosis.

A It's one of the factors.

Q And others might be case ascertainment?

A Yes.

Q Other factors might be bias selection, in a good way, people seeking out services, seeking out medical care, correct?

A Yes, so yes, it's clear that the diagnostic criteria, the way we evaluate autistic syndromes, has changed over time. That explains some of the increased numbers, but quite separate from that, the way we identify cases of autism, however we define them in populations when we do surveys, has also improved in terms of the efficiency of case ascertainment over time. Because of increased awareness, more studies have been developed and different social policies. So when we look at autism in a given population of samples, our capacity to identify the children has increased.

Q So we've got this very complex presentation of symptoms in a disorder that's entirely defined by symptom presentation. When we start looking, then, at

causation, if I recall, you discussed, and I'm not going to get into detail on this, but just to really try to focus us again on what the epidemiology is looking at, you talk about the genetics. And if I recall, at some point in your testimony, you indicated that as many as 20 different genes might be implicated in the etiology of autism. Is that approximation of 20, is that a fair re-statement of what your opinion would be?

A I don't recall having said exactly that.

Q I'm not trying to play gotcha, so aside from whether you said it or not in your testimony, would the involvement of potentially 20 different genes in the etiology of autism, would that be a fair statement of your understanding of the genetic contribution?

A I often quote one of the studies that was done in the U.K. as part of the family study of autism that we did at Maudsley and the twin studies. So we are a group of investigators, and we actually had a large data set looking at the rates of autism in first, second, and third degree relatives.

The falloff of these rates allowed us to develop models which predict how many genes are likely to be involved in our models, and I could quote an article by Pickles et al. in 1996. In our best

prediction, actually the five genes model was the most parsimonious model to explain that. But it was anywhere between --

Q I'm sorry, most parsimonious?

A Yes, the most parsimonious model. Our data were consistent with anywhere between three to up to 15 or 20 genes. Neil Rich in the U.S. has done other kinds of modeling techniques. In India, it's quoted like more 15 or 20 genes. So I don't know, but yes, a fair number of genes.

Q And so, to the extent that genetics has a contribution, you have a potentially complex genetic interplay, because potentially, at least hypothetically, you could have one individual who has been diagnosed with autism that has one gene implicated. You could also have another person who has multiple genes, and you could have people with any combination of genes in between, is that correct?

A Yes.

Q So, in the etiology, in the genetic makeup, complex subpopulations defined by their genetic make up correct?

A When we know the genetic make up, yes, we will be able to work backwards to the phenotype and try to dissect the phenotype in a more efficient

fashion. That's right. Yes. At the moment we assume that genes contribute a lot to the population science of this condition, but we assume that there is genetic heterogeneity, meaning that genes will be different in different families or cytogenes will be different in different families.

Q So you have genetic heterogeneity and you've got symptomatic heterogeneity within the populations of autistic people, correct?

A Yes.

Q And you used the word phenotype. I don't know if you're using that in a technical way, but I use the word subpopulations defined by say genetic make up or defined by a particular cluster of symptoms. Does that description make sense to you, having subpopulations within the larger world of autistic people who are defined by the genetics, assuming that we discover them, and by symptoms?

Is that a fair statement that there are these little subpopulations?

A Yes. I would not call that subpopulations, but I would call that phenotypes or endophenotypes, and then the genetic pathways through these different phenotypes or endophenotypes are likely to be different, and there might be several.

Q Okay. I'll go ahead and adopt your term because, again, I really am looking to avoid semantic confusion, and I appreciate your offering phenotype as sort of a working definition of what I was attempting to describe. Now, epidemiology. To really give you a picture of association one of the things that epidemiology needs to have is a measure of specificity. Isn't that correct?

A Depends what you mean by that.

Q Well, I mean, just in general. I mean, you're familiar with the Bradford-Hill criteria, are you not?

A Yes.

Q And the Bradford-Hill criteria are a list of criteria that one applies to epidemiological studies to see how well those studies actually describe the association that they are attempting to describe, correct?

A Yes.

Q And one of those criteria is specificity, correct?

A Yes.

Q When we look at the epidemiology that's been done so far on autism you've described some studies that break autism down by a type, core autism versus

atypical autism. Do you recall that description?

A Yes.

Q You describe autism early onset versus autism regression or autism late onset. Do you recall that?

A Correct.

Q By my count there were maybe, maybe, five or six symptomatic phenotypes of autism that these epidemiological studies address, things like early onset, late onset, symptoms of bowel disease. Is that a fair statement?

A Yes. No. I think that you're taking a step forward which I will not take. I'm not saying that these are different phenotypes. You are dealing with a behavioral syndrome, and then you look at correlates of these syndromes where you can have GI symptoms or not, you can have sleep disorder or not, you have ADHD, hyperactivity, or not.

It's not because you can stratify your sample by clinical characteristics of this stratification as meaning for causation. So in that sense it doesn't mean that when you do that you are prescribing two different phenotypes.

Q But isn't it true that with a population that potentially has hundreds of different phenotypes,

genetic expressions, symptomatic expressions, of an autism disorder wouldn't one want to have epidemiology specific to those phenotypes or subpopulations as I said? Wouldn't that be more specific?

A It would be more specific if we were in a position to validate endophenotypes, the subsamples, in a significant way. So far we have failed to do that in most research enterprise, so we don't have a good way to dissect today the phenotype into subphenotype or endophenotypes which would be more informative for etiological research or for other types of research.

I mean, there are ways to do that. For instance, you could take the example of language delay, for instance. Language delay is often associated with autism, but not always. So Asperger there is no language delay, and not all cases of autism do have language delay.

When we look at results of genome scan and linkage analyses, for instance, if we stratify some samples by the coexisting presence of language delay or not then you have some linkage signals which vary suggesting that some genes that we have identified in these linkage studies might actually be genes which control language development as part of autism. So we

are getting there in some studies, but there is no consensus on how so far to dissect them.

Q Right. You're talking about one way to go about that is to look at the underlying genetic component and have as a hypothesis there might be the genetic link.

If I was to posit that there may be links between specific symptom groupings or phenotypes, as we informally defined it, or subpopulations, if you wanted to look at clustering those symptoms together in ways that reflect the way they appear in a population and mash that up to vaccine exposure there actually at least in the United States is a way to do that through the Vaccine Safety Datalink, correct?

A I'm not sure about the VSD, what you can do with the VSD and how you can define or refine. I'm not sure what kind of data are there.

Q So it would depend then on the data. If the VSD did, for example, have *ICD-9* or *ICD-10* coding for discrete symptoms that would be useful. Things like language delay, attention deficit, those sort of symptoms that one might see in an autism population, those sort of symptoms are captured diagnostically in the VSD, correct?

MR. MATANOSKI: I think Mr. Powers' question

needs to first establish a foundation for Dr. Fombonne to speak about the VSD.

SPECIAL MASTER HASTINGS: Well, let's see if he can answer the question.

THE WITNESS: Sorry. Can you repeat the question?

MR. POWERS: I knew you were going to ask me to repeat it. The question is isn't it true that the VSD does have *ICD-9* and *ICD-10* coding for discrete symptoms including symptoms one might find in the autism population?

THE WITNESS: I believe it does, but you have to look at the holistic code in *ICD-9* and *ICD-10*. If a child has autism, you would not necessarily code with separately symptoms which are like free floating, or like language delay, or ADHD. So in a way the language delay is incorporated in the *ICD-9* autism diagnosis. So I'm not exactly sure what your point is.

BY MR. POWERS:

Q Right. At some point it might get captured by sort of the ultimate diagnosis of autism, but unless a diagnosis of autism is made that would capture all of those, again, it's not a trick question, it's just as far as you know sitting there

does the Vaccine Safety Datalink contain *ICD-9* and *ICD-10* diagnostic coding for symptoms that would be part of the autism spectrum disorder?

A No. I would challenge the last part of your sentence. No. You need some further evidence to say that they would be part of autism. Again, language delay is not a necessary component of autism, so there is a degree of sensitivity and specificity in terms of the prediction of the symptom to the final diagnosis. So it can be, cannot be.

Q One way that it could be, for example, if you looked at a population study that examined a hypothetical link between a particular vaccine exposure and you looked at the *ICD-9* or *ICD-10* coding in the VSD let's say that you came up with a significant number, we'll call it *N*, of people who have autism. Hypothetically you could do a nested case control study within that cohort, could you not?

A To assess what?

Q To then go back through and see if that *ICD* coding for autism included particular symptoms because then you would start to do chart review and record review. Is that correct?

A You could do a nested case control study in the cohort, yes, that's for sure, but I don't know

what would be the hypothesis, what will be your methods, to test what kind of ideas.

Q I'm not trying to propose a study here. That's way beyond my capability. All I want to determine is if you recognize that the Vaccine Safety Datalink in the United States provides a tool or an opportunity to link vaccine exposures to populations of people with autism both at the *ICD* code for autism and then getting into it with things like case control studies nested in a cohort.

Is that your understanding of what's possible with the VSD?

A You said different things in the same sentence, so, yes, I think the VSD allows you to look at the relationship between vaccine exposure and an outcome which will be autism as defined in *ICD-9* or *ICD-10* in the codes existing in the VSD database, that's fine. Now, the other thing you said, you could probably look at vaccine exposure in relation to other outcomes which are independent from autism.

I didn't say part of autism, I said independent of autism.

Q Right. Now, you've got this complex symptomatic presentation with a complex genetic component. In talking about the genetics I was

reading through your expert report and there was language as I went through there, I'm hoping I can find it, where I was looking for language where you might say that genetics are the cause, singular, of autism, and I didn't find any language like that.

So as I read your report I came away with the understanding that genes may predispose one to autism. Is that a correct statement of your opinion in your report?

A I don't know what you are referring to.

Q In general.

A Okay. In general. Yes. I think in terms of the etiology of autism what we know is that genetic factors play paramount contributions to the development of autism as estimated by variabilities stimulated from twin studies. Whatever your calculations are current variability estimates for autism are anywhere between 92, 93 percent, which indicates that 92 percent of the population's variance of this heavily defined disorder are accountable to gene effects, okay?

Q Right, yes, but not all of it. Not all of it. There's no evidence to support that autism is entirely a genetic collection of symptoms?

A Well, it's actually a bit more complex than

that. I mean, if you had 100 percent of variability, yes, everything would be ascribed to gene effects of one sort or the other. The fact that the variability estimates are slightly lower than 100 percent, you can see this discrepancy as two ways.

It could be measurement error, so it could well be that in fact it's just because our measures, our phenotypic measures, are poor and that we don't capture the whole range of the phenotype. In fact, if you were able to do that, actually, the variability would go up. And in fact, this is what happened in the history of autism.

When we looked at twin studies, like if you look at concordance rates between -- and -- twins, the concordance rate for them in the twins is about 70, 80 percent depending on the study.

So at that time you could have said there is 20 or 25 percent of population variance which is attributable to other, i.e., environmental factors, but then when we look at the nonaffected cotwins we found out they had what I described last week as being this broader autism phenotype which is a kind of mild phenotype critically associated with autism and sharing the same genetic propensity.

When we add this broad autism phenotype then

the variability estimates shoot up to 92, 93 percent. It could well be that the remaining persons which are unexplained in this model actually are reflecting measurement error in our capacity to measure the milder forms even of the first. So that's a notion which cannot be barred, but you could as well say then maybe there is some kind of room for environmental factors.

If that is the case the question is what it is. It's not very likely in the sense that, you know, fraternal twins compared to siblings -- these are twins, for instance -- have more of the same environment than siblings because they grow up in the same pregnancy, same wound, et cetera. So we would predict that if there were environmental factors, particularly those occurring during pregnancy, they are more shared by fraternal twins than by siblings.

Therefore, you would expect that the risk in these fraternal twins for autism would be slightly higher than there is for siblings from different pregnancies. In fact, it's not the case. So it's a way to look at environmental factors and their role in the genetics of autism, and the data are not very supportive of that.

Q But certainly that issue is as open as the

purely hypothetical one that the only reason it's not 100 percent is that we don't have the measuring technology to get there so that the door is open for an environmental contribution. I think there's even been testimony by other Respondent experts.

Dr. Cook I believe offered some testimony when he spoke. Yes. It's up on the monitor. This is page 1552. This is Dr. Cook's testimony. There was a question by Special Master Vowell about environmental -- type gets very big when it gets blown up on the small screen -- things triggering gene expression.

Dr. Cook said that environmental events can trigger changes in gene expression. I assume you don't take issue with Dr. Cook's statement, and that you would agree with that?

A Yes. No, I agree.

Q I'm sorry. I just couldn't hear you.

A Sorry. I agree with him. He's certainly more competent than me to speak about this genetic issue.

MR. MATANOSKI: Your Honor, before the next question I permitted the questioning to go on about genetics to go on for quite a while hoping that there would be some tie to it at some point to epidemiology, so if there's going to be a proffer that this is going

to be tied to epidemiology I'll be happy to let it continue, but if there's not then I think he's beyond the scope of direct, which was fully limited to the discussion of epidemiology.

Dr. Fombonne testified last week, he was subject to cross-examination then. I don't believe his testimony in fact went much into genetics last week. I also note that when he's being cross-examined about Dr. Cook's testimony that was taken out of context. Dr. Cook's testimony about environmental triggers was going to environmental triggers primarily prenatal and not the postulate here.

MR. POWERS: First off, I didn't offer any postulate excluding prenatal. It just was offered for what it was offered. The connection with epidemiology is that this expert has submitted an extensive report that links together questions of causation with epidemiology. His direct testimony today and the extensive Power Point presentation that accompanied it goes to these issues of causation.

It simply is I think as a practical matter impossible to untangle the threads of causation that are posited in this case from the epidemiology testimony, and there will be questions in epidemiology about confounding and environmental contributions,

what has been looked at, what hasn't been looked at, how that fits into the reliability and the specificity of epidemiology.

I'm not trying to replow ground that's already been covered, but when we talk about an admittedly complex etiology with very complex epidemiology attempting to describe it it's only fair to get into at least an overview discussion of the causative issues that are at play.

MR. MATANOSKI: And as Mr. Powers pointed out to Dr. Fombonne already genetics is not discussed in his report regarding epidemiology.

SPECIAL MASTER HASTINGS: Well, it is discussed in the part of his report on describing generally the causation of autism, so I'm inclined to give some leeway here. Go ahead, Mr. Powers.

BY MR. POWERS:

Q Now, one of the issues that you spoke about, and let's talk directly about epidemiology and causation, and particularly the genetic causation. Because I didn't see them in the presentation today had there been any epidemiological studies in the United States looking at the occurrence of autism in genetically high risk populations, that is within families who have people with an autism diagnosis?

A Yes.

Q And did those studies include an assessment of possible environmental contributions?

A I would have to look back. When I said yes I immediately thought about one of the first epidemiological studies in the U.S. done by E.R. Ritvo, it's called a UCLA-Utah study, where they actually documented for the first time I think the increased risk of siblings of autistic problems which was I think estimated at 10 percent in that study, and that's a study which goes back to the mid-1980s.

So that was a study which was epidemiological in nature and documented an increased risk in first development of autistic problems. So that was done. In that study, they looked at the role of perinatal factors. I don't recall that they looked at the role of perinatal or obstetric factors in relation to siblings affected with the disorder as well.

Q I'm sorry. You just don't know or is it your recollection that it did not?

A No. I don't recall if they did or not. Just to answer further your question there are ongoing studies, I mean, groups of U.S. investigators which are looking at the risk of autism in siblings, and

they use longitudinal studies for that. There is a BBC network to which many U.S. contributors are associated now.

Q In your earlier testimony I believe you described that the mom's exposure to rubella in the first trimester was known to cause autism spectrum disorders in the child. Is that correct?

A Yes.

Q How was that evidence developed? Was that developed based on epidemiology or is that a series of case reports that led to the conclusion?

A No, it's based on epidemiological calculations. It's based off on the accumulation of a quite substantial number of cases which were investigated which allowed the investigators to derive a rate of autism in children affected with congenital rubella, and this rate was subsequently compared to known population rates to indicate that there was an increase in the risk. It was not a simple collection of cases.

Q Exactly, but the initial conclusion that this was happening was a series of case studies, and the epidemiology came later really more as a compilation of what had been revealed in the series of case studies, correct?

A Unless you do the confirmation there is no conclusion.

Q Yes, but my question wasn't do you need to do a confirmation, it's just a simple question of which came first. My understanding is that it was a series of case studies that built the evidence so to speak. It was then later confirmed by population studies, correct? That was the sequence?

A No. No, no. It was just the examination of a large sample of children with congenital rubella, the measurement in the children of an autistic syndrome and then the quantification of the syndrome in that population, comparing that estimate to what you would predict should there be no association between autism in there and showing that there was an increased prevalence if you wish. So it's all the same step. The confirmation does not exist if you just have one case.

Q Right, because you would never pick up that signal in a large population if it was just one. I mean, it's hard to imagine a study that would have the power to pick up one idiosyncratic case.

A It's just that in medicine when you have an unusual observation a case report is not informative for causation in general.

Q Right. Right. Except perhaps to develop a hypothesis that then can be investigated.

A You will have to have some particular specific studies, first observations, before you can even talk about it because we observe patients -- I see patients all the time when they're small. I had one who had early puberty where he was six years old he got pubic hair developing, so I could say I have identified a subphenotype of early pubic hair autism phenotype, no?

It doesn't work like that because in medicine we see a lot of things which are cooccurring with a disease or the condition we deal with, and most of these observations are just random or indefinite findings or correlates.

So before we start to be interested in the unusual observations there needs to be either something which is quite unusual and specific unknown to what you observe or you need to accumulate a large enough studies of cases to start to document this unusual phenotype. It takes a lot of time.

Q Yes, I understand. It definitely takes a lot of time. I mean, probably science and law together work at a pretty slow pace. You talked about thalidomide exposure, that's a prenatal exposure, an

environmental exposure, that has been known to cause autism. If I recall it was thalidomide exposure between days 20 and 24 of the pregnancy. Is that correct?

A Correct.

Q And sort of the same question again. The fact that we know that came from looking at case studies, and it's not something that there was some cohort study that was investigating the hypothesis that thalidomide exposure might cause autism. That didn't happen first. There were case reports that then led to the generation of this hypothesis and the methodology to confirm it. Is that correct?

A No, it's not correct.

Q So there was a large cohort population study, and it was that study that was then able to identify these thalidomide cases that arose from days 20 through 24 of pregnancy?

A I don't know what you mean by cohort population study. As I recall, there was this use of thalidomide in various countries, and in Sweden in parts used, so there were children exposed to thalidomide, and there was a large sample of them who were subsequently followed up, okay?

Q About how many?

A I don't recall, but it was not a large number. The paper is in Stromland, 1994, and can be looked at. So they were followed up, and then they were examined and then it was found that some of them did have autism.

Then people actually looked at the rate of autism in these cases and found that it was increased compared to what you would expect under the assumption of independence between the two conditions, and particularly when they narrowed down the phenotype to those who had autism but didn't have limb abnormalities. That's how they came up with this time window.

Q So I want to talk a little bit about the *DSM-IV* criteria that you were describing earlier today and some specific questions about that. Now, the *DSM-IV* diagnostic criteria, is that a diagnostic method or is it a criteria? Again, because I'm not trying to play word games, I really just want to make sure we're speaking the same way.

A No, no. It's an important question. It's absolutely not a diagnostic method. There is nothing in the *DSM* or nor in *ICD-10* which tells you or a clinician how to evaluate a child, so it's left up to you. You can just walk in the waiting room, observe

the child, make up your mind, and if you have enough symptoms you can score *DSM-IV* criteria and then reach a conclusion.

Sometimes, you know, when I walk into a waiting room and see a child who is waiting to see me sometimes it takes me three minutes to know that he has autistic disorder, but in many instances it will take me more like two or three hours for an assessment, so it will vary according to the child. But the method that the clinician uses to evaluate the symptoms is left to your choice.

So it could be regular clinical examination or more standardized observation or measure, developmental interviews, which are there just to guide the clinician in the collection of informative symptoms both now and in the development which can be then used to apply *DSM-IV* criteria, which is basically an algorithm to reach a diagnostic conclusion.

Q Okay. Now, the *DSM* criteria that you're describing is *DSM-IV*. That's currently in use in the United States, am I right?

A Yes.

Q And is that used in other countries?

A It is used in other countries, but in many other countries *ICD-10* is the preferred diagnostic

nomenclature.

Q What are the differences between *DSM-IV* criteria and *ICD-10* criteria? One of the reasons I'm asking that to make it clear that this is actually connected to the epidemiology is that we're looking in many cases at studies that were conducted in other countries relying on data and diagnoses in other countries, so perhaps you could explain the difference between *DSM-IV* and *ICD-10*?

A Well, I mean, a major difference is *ICD-10* is a global nomenclature system which allows, you know, all sort of institutions, government, to produce morbidity statistics across the board. So *ICD-10* deals with a whole range of medical disorders, cancers, you name it, everything is there.

Q When you say global, is *ICD-10* an attempt to get a common language that practitioners wherever they may be in the world can use so they all know that they're talking about the same thing?

A It's meant to provide a common language to practitioners, common diagnostic systems, across countries. It's also meant to provide a common reporting system for important vital statistics in many countries. So it's real important. And *ICD-10*, unlike *DSM-IV*, covered a whole range of medical

disorders. So in *ICD-10*, you have one chapter which is called Chapter *S* if I recall which is dealing with psychiatric disorders. So that chapter, which is just a tiny part of *ICD-10*, is comparable to *DSM-IV*, which also is only dealing with psychiatric conditions.

Q Yes. And I've seen the *ICD-9* book, and yes, I think it's the 200 series, like up to 299 is autism?

A Yes.

Q You sort of then go back down and there are components in there, but it's in that same chapter with the same three digit prefix, correct?

A Yes. I don't know which chapter it was in *ICD-9*, but yes, 299.0 is autism, 299.1 CDD.

Q Okay. Now, the studies that you talked about today were conducted in if I recall the U.K., Japan, Denmark, the United States and Canada. Were there any studies conducted outside of those five countries? I'm not saying just in general but that you talked about today or that you relied on.

A There was a Swedish study I think I mentioned. I think other than that you're correct.

Q So it would be Denmark, Sweden, Japan, the U.K., Canada and the U.S. Which criteria does each of those countries use to record their diagnosis of autism, *DSM-IV* or *ICD-10*?

A It's variable. If you look at the studies I published when I was in the U.K. I published them using *DSM-IV* criteria. Many research groups would use *DSM-IV* criteria when they conduct their studies. Actually, the reason why in autism you would use *DSM-IV* criteria is when you want to submit your article to an American publisher. That's the main reason to do that because people in --

Q And if the rule is published for Paris there's a strong incentive to use the *DSM-IV*?

A Yes, exactly. So *ICD-10* is otherwise used often in European countries, but also, *DSM-IV* investigators use both systems. In fact, if I extrapolate on your questions as far as autism is concerned the differences between the two schemes are really minor. There are some, but they are not impressive.

Sorry to interrupt you, but you can actually collect data, score them in *ICD-10* and then transfer the codes in *DSM-IV* quite easily with a few exceptions.

Q And the idea would then be that there would be global uniformity in your diagnostic definitions, correct, so that any diagnostic conclusions that you reach, whether it's in the U.K. or wherever, can be

matched to other diagnostic conclusions in autism anywhere in the world?

A Yes. I think I mentioned last week I was part of this working party which I was representing WHO with Michael Rutter in 1990 and 1991, and we met with the child psychiatrists working party of the American Psychiatric Association which at the time were revising the diagnostic criteria for the whole child psychiatric section of *DSM*.

So we worked together for at least a year with using cross-walks and meetings to make these two schemes, which were in preparation at the time, *ICD-10* was preparing, *DSM-IV* was preparing, to make them the more alike that we could in terms of the concepts, diagnostic criteria, algorithms and wording. We succeeded to a large extent compared to the previous situation to make the two schemes quite comparable, but there are some areas where there are, you know, discrepancies.

Q I understand the areas of discrepancy, and if I recall from your expert report paragraph 29 discussed two studies that you cited for the reliability of diagnoses across countries. There was Volkmar and Filipek. I know you didn't discuss those today, but there was a 1994 study and a 2000 study.

Are you aware of any other studies or investigations that have been done to make sure that *ICD-10* coding and *DSM-IV* coding for autism are in fact reliable and consistent from one country to another? Have any other studies besides those two looked at the reliability issue?

A You must specify what you mean by that. The reliability issue in the context of across countries use?

Q Yes.

A Well, it depends what you mean, but the 1994 et al. paper by Fred Volkmar was in fact a late publication, but it was a study. I was part of the study, actually.

We collected data as early as 1988, 1989, 1990, and the idea was to ask various expert groups in the world to write -- basically what we were asked is in our clinical practices to see autistic children the way we are seeing them, collect some data, IQ data and whatever we needed, but then to apply after the conclusion of our clinical examination various diagnostic schemes.

In other words, we used *DSM-III*, we used *DSM-III-R*, we used the draft guidelines for *ICD-10* and we used the draft guidelines for *DSM-IV*. Then the

idea was then to compare how each diagnostic scheme was performing in relation to each other and in relation to a growth standard, which was the clinical judgment, which is always --

Q I'm sorry, which was?

A The clinical judgment. So at the end of the day you need a standard, a global standard, to assess our diagnostic schemes' performance, and in all these studies, in fact, it's quite surprising, but what is the global standard is the expert clinical judgment by people who know and assess children with autism. So that's how it was done.

We could look therefore at the sensitivity and specificity of different diagnostic schemes, and it allows us to look at how to organize the criteria, what would be the best algorithm which would work in the majority of the cases. So that is a typical study. It's an empirically driven study where we look at criteria, we look at reliability, we look at validity.

MR. POWERS: Well, doctor, I want to direct your attention, and maybe folks at Respondent's table, since we just have paper copies of the presentation today could get these up on the screen for me so that everybody can see what we're referring to?

BY MR. POWERS:

Q This is Respondent's Trial Exhibit No. 21 for the record, and that would be the slide presentation that Dr. Fombonne gave earlier today. To start off with I wanted to direct your attention to Slide No. 5. Do you see Slide No. 5 in front of you there?

A Yes.

Q You recall this is a slide that reflects some of the results of a CDC study on autism prevalence in eight year olds, correct?

A Yes.

Q That study concluded that there was an average across 14 states of 6.6 per thousand, correct?

A Correct.

Q Now, that average takes into account a low in Alabama of something that looks to be just over three per thousand and going all the way up to New Jersey which looks to be just over 100, correct?

A Ten in your --

Q Yes. To use the right number of decimal points it would be 10 per thousand as opposed to three per thousand.

A Yes.

Q So by aggregating this data and presenting

it as 6.6 if one looked only at the 6.6 one would have no idea of knowing within these 14 subpopulations what the prevalence rate actually was in each of those places, correct?

A Of course. I mean, this is an average, but there should be a measure of dispersion associated with it which should be a standard deviation, yes.

Q And it looks like based on the color of these bars that four states -- well, certainly three of the four states on the far left have prevalence rates that are lower than even the lowest of the 10 states to the right of the chart, correct?

A Correct.

Q And I notice that in the colored bars those are states where the numbers were generated from health sources either exclusively or almost exclusively, correct?

A Correct.

Q How can one explain the difference between prevalence rates based on health sources versus prevalence rates derived from education sources, particularly when you have a rate that is 300 percent difference between say Alabama and New Jersey and a completely inverted ratio of health sources to education sources? Any idea of how that might be

explained?

A Well, it's not the way it works. I mean, the way it works is you do your study and they use a common set of methods to identify cases in all states. The methods include scrutinizing school records, going through medical records, hospital data. So they apply the same techniques to find cases in all states, and then they find what they found.

Then what they did is in their sample for each state they looked at what was the source of identification for each of the cases. So it works in that sequence. Then what you said is correct that in the states on the left most of the cases ultimately were identified and contribute to the numerator of this prevalence rate were identified through health sources as opposed to educational sources.

As you can see, even on the 10 states which are on the right-hand side there is variability. So New Jersey and Maryland are different in terms of the proportion of cases which are identified primarily through an educational source or a health source. That reflects the interplay between health services, educational services, which is highly variable, as it's clear in the U.S., but it's true in other countries as well.

Q That variability then, if one was just looking at the 6.6 per thousand across 14 states just as the variability and prevalence would be obscured by that average the variability of where the data came from would be obscured by simply stating the average, correct?

A Sure. Sure.

Q So when you aggregate data you tend to lose information specific to some components that underlie that data, correct?

A You lose information, but it's a way to convey a single message base on a study. Even if there was no such systematic difference, seems to be the case, there would be still some variability. If you look at the states on the right-hand side, you know, not every point is the same, so there is variability.

It's part of the random situation that each study comprises. So there is variability in each estimate. So if you aggregate then of course you should provide a measure of range of dispersion between your results to convey the full information, but that's what they did in this picture and other tables in their documents.

Q Let's look at Slide 7 if we could. Now,

Slide 7 as I understood it was that in Finland they took a group of children between the ages of 15 and 18 years old and they looked first to see if you applied the old Kanner diagnostic criteria what your rate of autism would be, and then applied *ICD-10* or *DSM-IV* for autism as a discreet component of the broader spectrum and then finally autism spectrum disorder, correct?

A Yes.

Q In doing that the rates go from 2.3 per 10,000 to 7.6 per 10,000, correct?

A Correct.

Q If I recall your testimony you said that the generally accepted prevalence rate for autism spectrum disorders that's recognized currently is roughly 50 per 10,000. Is that a correct statement of your testimony?

A In population surveys recently, yes.

Q I was just curious looking at this slide, with applying the *ICD-10*, which is the currently used global standard, and *DSM-IV* it just seems that one would expect to see a number closer to 60 than 7.6 leading to the question, what happened to the other 52.4 people that you would expect to see there?

A Well, let me explain to you a few things. The study is published in 2000, all right, and it's

based on a kind of registry which is existing in Finland, so it's not the type of population survey where you screen very actively to identify cases in a particular area, it's more like this type of a standard study statistical data that you have in many countries, so that would in itself lead to a lower figure.

Then if you look at the age the study is published in 2000. The data might have been collected in let's say 1998. So these subjects were born in 1970 so that they will be having a lower rate in terms of at age 15 or 18 is not entirely surprising considering that they were born in the early 1970s.

So that doesn't surprise me. But the point of this study, the message is completely irrespective of the absolute way they define. What is important here is to look at the variability in the estimates based only on the variation in the algorithm that you apply or the diagnostics system that you apply.

So whether or not they have low rate or high rate in their study is irrelevant here. What matters is that there is internally in that deficit you can see that you can have a tripling of your prevalence rate by just applying different sets of diagnostic criteria, everything being equal otherwise.

Q Yes, but even going back and sort of drilling down so to speak within that cohort where the records were available you still are left with a rate that is several orders of magnitude lower than one would expect if one was looking at a 15 to 18 year old group of people today.

A Yes, probably. The study has to be done.

MR. POWERS: I realize the time coming up on 12:25. I have a significant number of questions still to ask, and I just wanted to interrupt myself here to see how the Special Masters wanted to schedule today. I have at least an hour.

SPECIAL MASTER HASTINGS: Let's go until 1:00 or around then if there's a breaking point somewhere around there.

BY MR. POWERS:

Q Okay. So let's continue moving through the report then. If you look at Slide 13, now here on Slide 13 as I understand it we're looking at prevalence that's based on U.S. Special Education Services, correct?

A Correct.

Q If I recall, earlier in your testimony you said that education social service referrals were not a good reliable source of prevalence data. You had

slides on that.

A Correct.

Q So in one slide it's not a reliable source of prevalence data, but then in Slide 13 it's reliable enough that you're using it to support your hypothesis of diagnostic substitution, correct?

A Yes. Well, these are two separate questions. I showed, and everybody would agree, that using this type of data will not be useful to assess population rates and trends over time in population rates.

Q Which is incidence, correct?

A No. Prevalence or incidence. These data do not allow you to calculate unbiased estimate of the true population rate be they incidence or prevalence, okay, and therefore, they are inappropriate way to evaluate time trends and test hypotheses about an epidemic. If we can go back two slides before the reason is that one, the author actually at the inception of this study he just makes this general statement and comment, says well, let's look at the data from the Department of Education in the U.S.

We know we have this data and these trends that some people claim are alarming and showing that there is an epidemic. It says well, actually now we

have U.S. population surveys done by the CDC which give us a reasonable range for what is likely to be the true population rate or something which is close to that, and it gives two studies which are providing a minimum rate of 34 and a maximum rate of 68, which is based actually on the breakdown sheets of CDC.

So the true prevalence, which is something we know based on these two studies, is anywhere between these two horizontal lines. He says then let's look at what kind of prevalence estimate we can obtain if we just use the Department of Education data. It says in 1994. If we just look of the Department of Education data, the prevalence that we would infer would be six per 10,000, which is much bigger what it is in everything.

Because this rate is so low, of course as time goes by, only an increasing number of children will be captured in this newly formed educational category of autism, and at the end of the study he comments on the fact that in 2003 even then the mean rate that you would extrapolate if you use this Department of Education data is still lower than the minimum population rate which is low when you do proper population surveys.

So the point here is that you say anything

which is going up in this trend is not telling us about what's happening in the population because it started very low, it hard to capture, but this is what's happening.

Q But this is educational data not medical diagnoses, correct? These are educational referrals not *DSM-IV* diagnoses?

A No, and as I understand the Department of Education Special Education Office requires this data about children with autism. I think they refer in their documentation to the concept of *DSM-IV*, but they actually do not require that children would be evaluated with *DSM-IV* criteria. It's left pretty much to the freedom of each state to actually define who is eligible for this category, who is not.

That fluctuates from state to state, that fluctuates over time within the same state. So it's pretty loose in some ways.

Q Yes. So I just want to refocus the question then because I thought it was a simple question. The prevalence rate here is being computed by an educational definition of autism and not necessarily by a *DSM-IV* definition of autism, correct?

A These are children who are in the educational system with a recognized special

educational need in the autism category which was set up as a separate category in 1993.

Q Okay. So it sounds like one of the things you're trying to do from prevalence looking at point prevalence like within a birth cohort at a particular period of time or the cumulative prevalence, which I guess is adding up the prevalence rates across several different cohorts and coming up with an inferred incident, that is inferring what the rate of autism occurrence is within each cohort over time because we really don't have anything on incident rates epidemiologically, do we?

A We do. There are some incidence studies, pure incidence or cumulative incidence data, but in none of the existing studies. Well, we did one in the U.K. with using the GPRD database where we had this huge increase in incidence rate, particularly for the PDD risk category, but most incidence data which exists has failed to control for any change in case ascertainment or case definition.

So the fact that there are trends up are not really particularly informative. There is a good study by Barbaresi in the Rochester Mayo Clinic registry which shows increased cumulative incidence. That's one of them.

Q So is it your opinion that any increase in the incidence of autism in the United States is entirely due to diagnostic substitution, expansion of the *DSM* criteria and better case ascertainment? Does that completely explain the incident rates of autism in the United States in your opinion?

A No. My opinion is actually not that one. My opinion is that, you know, I think it's fair to say that the best estimates we have today are the figures I gave based on a number of studies. So the prevalence rates have gone up over time it's very clear.

I think it's clear, too, that we can demonstrate in many countries that a large proportion of this increase in prevalence figures is due to a combination of broadening of the concepts of autism, changes in diagnostic criteria, which is much larger now than they used to be and we have empirical demonstration of that fact, and that over time there has been an increased awareness, the different social policies, better services developed in most countries and therefore facilitating the sensitivity of capture of autistic disorders when you do surveys.

So these phenomena are shown to contribute to the increase in the prevalence figures. I think

there is no doubt about that. Can we say that all of the increase in prevalence is entirely accounted for that? No, we cannot be sure about that. It's true that the magnitude of these methods, in fact we are fairly certain that in theory, it could explain it all, but there is no direct demonstration that it is the case.

So the hypothesis that there might be something in the environment, for instance, which might be contributing to a small extent to these increased prevalence figures, still needs to be entertained. That's why someone like me who has an interest for these ideas does research on this hypothesis.

At this point in time I must say I want to complete my opinion, and I was in the planning committee of the recent Institute of Medicine special committee or seminar on environmental factors. At this point in time there is no clue or no lead in terms of a real good candidate in terms of environmental factors putting aside the immunizations hypotheses, which in my view have been dismissed.

Q Yes. I think it was in April there was a couple of days that the IOM had these meetings here in Washington, D.C.

A Yes. Correct.

Q There will not be a formal consensus paper coming out of that as I understand it, but there will be a work group or a study group moving forward to take some of those recommendations and explore them. Is that correct?

A Yes, that's correct.

Q Perhaps some of that information would be able to be available to the Special Masters here as these test cases proceed. Mr. Green just flew out there. So what you're describing as this IOM meeting is something that the Special Masters may here more about down the road if these cases proceed. Doctor, are you familiar with Craig Newschaffer and the 2007 review study he did on autism epidemiology?

A I think I've seen it, but I'm not --

Q Yes. I think he's from Drexel University.

A Yes. I know who he is. I don't recall having read his paper.

Q Okay. So you don't recall whether you read it or you've read it but you don't recall the specifics?

A No, I don't think I read this paper. It's a review paper?

Q It's a review paper. You know, we actually

have it. We're prepared to introduce as Petitioners' exhibit whatever the next exhibit number would be on the list for Petitioners' trial exhibits. As we pass

that out, Doctor, since you haven't read it, you've made that representation, I'm not going to be grilling you, or quizzing you, on the content.

A Thank you.

Q But I just wanted to highlight one item in the study, and ask: If you think it's a fair statement, consistent with your opinion that you described on these issues, of what might be driving the increased prevalence rate of autism?

And what I'm looking at it, so you know, if everybody has a copy, is on p. 239, you see, Doctor, there are two columns of tax. In the right-hand column, the first full paragraph, which is a very long paragraph, begins with: The epidemiological data.

If you then look down to the bottom there, you'll see a sentence that begins: Nonetheless. And then continuing through the rest of the paragraph. If you could just read that portion.

A You want me to read it?

Q Yes. You could just read it to yourself, and then look up after you've had a chance to read it.

A Do you want me to read it?
Q Not out loud.
A Out loud?
Q No.
A Okay. Yes, I could.
Q Do you agree with the statement, Dr. Newschaffer's statement, about what explains the historical increase in the prevalence rates is accurate?
A Well, I mean, it's not inaccurate, but I think it doesn't seem to reflect some data which is more convincing in terms of ensuring that a large proportion of the increased prevalence figure can be explained by what we've discussed so far.
I'm going to complete my answer, just maybe get one of, this one, the third one. I would like to say --
Q On this, I was just asking because again, I don't want to do any ambush type thing where I'm asking you to comment extensively.
A You know, you're taking a paper by someone who is taking a particular approach, which is *prospectivement*, and I'd like to show you this one.
Q As you search for that slide, I will perhaps, for the benefit of those who are listening

and don't have the benefit of the exhibits, since it's a brief passage, if I may just read that, so that anybody who is listening in has an idea of what we're talking about, although it just got pulled.

I'll read it from the paper copy. The passage we're talking about here says: Nonetheless, the question of whether this historical increase can be fully accounted for, by these and other changes in diagnosis and classification, remains open to debate, largely because it is very difficult to develop quantifiable estimates of diagnostic effects; and virtually impossible to prove or disprove temporal changes in autism population risks profiles, given the condition's unknown etiology.

You've indicated that you agree in part but disagree in part with that.

A It doesn't say something which is vastly different which I said before. But I think it's plan is a bit looser; there are some data that it doesn't know or doesn't refer to, like the Kierinan study, I think it doesn't quote it, and others, which could be used to address the question he wants to address.

And I would like to show you just for the sake of completion that these -- it's not how is it?

Q No.

A That this --

Q I'm not sure exactly what you want to show us. You're going back to one of your slides?

A No. That's a new slide. It's a new slide. It's actually a slide of reference by very important people who are very well respected in their field. As you see here the name of Michael Rutter, who is probably one of the leaders in this domain.

All these people have looked at the autism epitome hypothesis and have concluded, pretty much, like I did conclude myself. So I think there is a body of scholars. We have reviewed this hypothesis and have concluded like I did.

SPECIAL MASTER HASTINGS: These are slides, as previously, where we decided for the sake of moving the presentation along, not to go through quite as much information as we had available.

MR. POWERS: I understand. We've marked Petitioners' Trial Exhibit 15, the Newschaffer study.

(The document referred to was marked for identification as Petitioner's Exhibit No. 15 and was received in evidence.)

SPECIAL MASTER HASTINGS: I guess if you

could at some point take this slide and mark it as Respondent's Trial Exhibit 22.

(The document referred to was marked for identification as Respondent's Exhibit No. 22 and was received in evidence.)

SPECIAL MASTER HASTINGS: Go ahead, Mr. Powers.

BY MR. POWERS:

Q Okay. We'll shift gears here a little bit, and start talking about some of the studies that you were describing in detail relating to the MMR.

If I recall your testimony, and reading the materials in Taylor, Taylor, the study, looked at it, the U.K. population, correct?

A Correct.

Q And that U. K population typically got their, and I think this was in your direct testimony, they got their MMR at 30 months of age, is that correct?

A Yes, it's usually between 12 and 15 months of age when I've reached -- he gives, I think, the average MMR immunization date in his study. It might be 14 months of age, I'm not sure. I'd have to check,

but it's between 12 and 15.

Q Now, the children, who were getting the MMR vaccines in the U.K. that were included in the study, those children were not getting thimerosal-containing vaccines in advance of the MMR to the same level that the Petitioner in this case received, is that correct?

A There are several questions in your question. Were they receiving thimerosal-containing vaccines?

Q Let's break it down. Were they receiving thimerosal-containing vaccines in advance of the MMR?

A Most certainly.

Q And most of them would have received it at the three-month, four-month, and six-month check-up, the DPT. Is that correct?

A Correct.

Q So, assuming full coverage and doing it one time by age six months, a child would have received approximately 75 micrograms of mercury as a component of the thimerosal in those shots before the MMR, correct?

A Of thimerosal mercury, yes.

Q Yes, so that's thimerosal mercury.

A Good.

Q So it would be 150 micrograms of thimerosal,

but 75 micrograms of mercury. So, again, to make sure we're talking the same language, I'm talking about the actual ethel mercury, 75 micrograms within six months, correct?

A Correct.

Q And then, between the ages of six months and between 12 and 15 months, they would have received the MMR, correct?

A Correct.

Q Now you're aware, I assume -- in fact, from your testimony earlier in this hearing, I know that you are, that Michelle Cedillo received significantly more thimerosal in her childhood vaccines before she got her MMR than did anybody in the Tucker study, correct?

A In the --

SPECIAL MASTER HASTINGS: Taylor, you said Tucker.

MR. POWERS: I'm sorry, Taylor.

THE WITNESS: Okay.

MR. POWERS: Again, I'm misspeaking, not being deceitful.

THE WITNESS: I know. Yes, correct. She would have received like more because the immunization schedule in the U.S. was different.

BY MR. POWERS:

Q And you're aware obviously, again, from your testimony and your expert report that a theory in this case is that the presence of a thimerosal-containing vaccines, at the point of life in which Michelle Cedillo received them, contributed to the MMR leading to her autism, correct?

A I'm aware of the theory; I'm also aware of the experts that we have heard, which indicate that there is no evidence for immune dysregulation induced by her initial immunizations.

Q Again, I don't want to be rude, but I do want to keep things focused on the question. I'm not asking you to recapitulate the testimony of other experts. I just want to make sure that we can focus on some of the specific theories of causation in the case in front of the Special Master, and apply these epidemiological studies to them.

So, it's a critical causation component of this case that the combination of thimerosal-containing vaccines, and the MMR, caused Michelle Cedillo's autism, correct?

A If you say so, yes.

Q And it is also part of the medical record that Michelle Cedillo received in excess of 180

micrograms of ethel mercury via thimerosal before she got her first MMR, correct?

A Yes, I believe so.

Q And the Taylor study has not a single child in there that has anywhere near that mercury exposure preceding the MMR, correct?

A Probably not.

Q So the Taylor study is completely silent on the thimerosal combined with MMR theory here, at least at the dose of thimerosal that we see in these cases, correct?

A Well, it does provide information about a lower dose of thimerosal than you mentioned. That's why I suspect it's informative to the debate.

Q Right, and I understand what it is informative of. But the theory of the case here, and of the potential cases that might be resolved, is that the U.S. vaccine schedule introduced a certain amount of thimerosal, and therefore ethel mercury that then set the stage so to speak for MMR.

The Taylor paper just doesn't address that thimerosal-containing vaccine schedule whatsoever, does it?

A It does provide some data, that she was exposed to some amount of thimerosal, not at the same

level that what you described, that's for sure.

Q And, certainly, not at the same time of the administration. Because, in England, in the U.K., the thimerosal-containing vaccines are basically all administered by the age of six months, correct?

A Yes.

Q In Michelle Cedillo's case, those thimerosal-containing vaccines were administered well after six months, right up until the time she got her first MMR, correct?

A Yes. I don't recall the exact immunization schedule in her case, but I think you're correct.

Q Then the Smeeth study that you talked about in the U.K., and rely on the MMR issues. Again, that's a population that didn't receive a thimerosal-containing vaccine schedule at a rate anywhere comparable to what Michelle Cedillo got, is that correct?

A Yes. I mean we didn't look at the thimerosal-containing vaccines. We have the data somewhere, but we never analyzed them in this respect. But as it's a U.K.-based study, it's correct to assume what you said.

Q So, the U.K. study just doesn't give us any information particularly the dosage on thimerosal-

containing vaccines, as it relates to a later dosage of MMR, correct?

A It does and it does not. You're right to outline some differences in terms of the U.K. and U.S. schedules. But at six-months of age, as I understand, the accumulative amount of ethyl mercury received through the U.K.'s immunization schedule is actually comparable to what is received by U.S. children, or was received by U.S. children, at six-months of age.

So it's the same amount by six months when the schedule is -- at six months of age, the amount of ethel mercury, through both schedules, is similar.

It's after that, that they diverge from what I understand.

Q And there's a timing issue that's different before them because Michelle Cedillo, and many other children in the United States, particularly children who have claims in this program, received a dose of thimerosal within 24 hours of birth, with the Hepatitis B. You don't have that exposure in any of the U.K. studies, do you?

A No, except in special circumstances, I believe.

Q Now, in the 2002 Madsen study, they looked at birth cohorts from 1991 to 1998, and looked at the

MMR issue, correct?

A Yes.

Q As I understand it, in Denmark, thimerosal-containing vaccines were completely phased out by the middle of 1992, is that right?

A Yes.

Q So you would have had a zero thimerosal exposure for the subjects in this study from mid-1992 all the way through 1998, correct?

A From 1993, or 1992, yes.

Q Right. At some point --

A Yes.

Q -- somewhere between mid-1992 and the beginning of 1993, you would have a birth cohort that had zero thimerosal-containing vaccines?

A Correct.

Q So, again, the Madsen case, completely absent any thimerosal exposure whatsoever, is absolutely silent on the proposition in this case that thimerosal- containing vaccines, combined with the MMR, caused autism. It has nothing to tell us about that connection, does it?

A It does. Actually, I did speak to my colleagues in Denmark, Madsen and Veet; and I had correspondence with them. They drew attention on one

part of their published paper, which I would like to show you as a response to your comment.

Can we have this last slide?

It's not large enough. Can you enlarge it?

MR. POWERS: We're both doing the same thing. For those at home, that was: putting on reading glasses.

THE WITNESS: This is a new slide.

MR. POWERS: I'm sorry, when you say new slide, is it an exhibit in this proceeding? Was it attached to your expert report?

THE WITNESS: No.

MR. POWERS: So that we can talk about it. Is it going to be a trial exhibit, perhaps we can mark it, if there are questions?

THE WITNESS: But this slide, this is a table which is contained in the Madsen, et al. 2002 article, published in the *New England Journal of Medicine*, so it's available.

SPECIAL MASTER HASTINGS: It's already in the record?

THE WITNESS: Yes, it's already --

(Multiple voices.)

BY MR. POWERS:

Q Okay. So this is directly from the paper.

It's not an additional complication?

A No, no. So the idea is that, on that table, you can look at the last block, if you wish, which is called: Date of Vaccination.

Then, here, you have basically a contrast, which is looking at the incidents of autism in various groups compared to a reference group; and the group here, the sample here, is stratified according to the date of the vaccination. The date of the vaccination here, the date of the MMR.

So, when the MMR was given. In the first years, 1991, 1992, in fact, these children were receiving thimerosal-containing vaccines. That's what my colleagues mentioned to me.

They said: This is the first group who were receiving both MMR and thimerosal-containing vaccines, as per the Danish schedule of immunizations, which was then in place.

Then, if one looks at 1993, 1994, that's the group which was more likely to have not had thimerosal-containing vaccines. In subsequent years, 1995, 1996, they didn't have any thimerosal-containing vaccines. They only had MMR.

You can see that when you look at the relative risk, they're no difference, whether the

children were exposed to MMR and thimerosal-containing vaccines, or without any. So, again, that provides a kind of taste of the combined exposure.

Q You can't tell from looking at this table, though, if all of those children who were counted as vaccinated, which is a number generated by the MMR, I don't see any data here that shows how many of those children actually received thimerosal-containing vaccines, and when and at what dose?

Was there information that's behind there that we ought to be able to look at?

A Well, yes, I mean there was. Sorry, I should have given that to you. The Danish investigators -- but firstly, when a family vaccinates a child with MMR, it's extremely likely that the child will have the other set of vaccinations. That's in general.

Secondly, the coverage of the TCV-containing vaccines was 96 percent or 97 percent, so you can assume with a lot of safety that most children who were receiving the MMR had also received TVC. There are at least 96 percent, 97 percent of them when TCVs were present.

Q Right. And I understand all of that. But, again, in terms of evidence in the record and what

we're seeing here, I just want to make it clear on the record that one cannot tell from the exhibit that's on the screen how many of the children who got the MMR also got thimerosal-containing vaccines. Correct?

A Correct.

Q You can't tell how many thimerosal containing vaccines they got?

A No, but you could assume that there was an upper limit.

Q Yes, certainly, it wouldn't have been any more than what? three under the Danish schedule?

A Yes.

Q So that the maximum they possibly cold have received would have been 75 micrograms by the time they got their MMR. But the data is not present in this table to give us information on that. Correct?

A Yes.

Q And the data is not available in the text of the Madsen paper, correct?

A Correct.

Q About here, correct?

A No, correct, correct.

Q Now, as I understand it, the NAS study also was a U.K. study, correct?

A Correct.

Q So, again, it's dealing with a population that didn't have a thimerosal-exposure pattern that would consistent with Michelle Cedillo's, is that correct?

A Yes, correct, I think.

Q The Kaye study, also U.K.?

A Kaye study, yes.

Q Okay. In the U.K., Kaye?

A Yes.

Q That study, again, same issue: Doesn't have the same thimerosal exposure that Michelle Cedillo, and other cases that are in this program, had, is that correct?

A Yes, it's correct.

Q Now, I want to talk about the study in Japan.

SPECIAL MASTER HASTINGS: Maybe this would be a good time -- you still have a substantial amount left?

MR. POWERS: You may not want to hear that, but I do.

SPECIAL MASTER HASTINGS: I want to hear the truth.

MR. POWERS: Yes, I do.

SPECIAL MASTER HASTINGS: Why don't we take

a one-hour break at this point.

MR. POWERS: So, at five until two, we should be back?

SPECIAL MASTER HASTINGS: Yes, and we can start then. Thank you.

WHEREUPON, a short recess was taken.

SPECIAL MASTER HASTINGS: All right. Let me make sure we're back in conference. Is the intercall operator there?

OPERATOR: Yes, sir, we're here.

SPECIAL MASTER HASTINGS: We're back in conference?

OPERATOR: Yes, sir.

SPECIAL MASTER HASTINGS: Thank you very much.

All right. We're back from our luncheon break. Dr. Fombonne is still on the stand, and Mr. Powers is going to continue with his cross-examination. Go ahead, sir.

MR. POWERS: Thank you, Special Master. As a quick note, I'm going to try to speak as loudly as I can reasonably project. My microphone has a dead battery. If anybody has a problem hearing me, let me know and I'll just do my best to compensate for the lack of technology.

BY MR. POWERS:

Q Now, where we left off before we took a lunch break was discussing, if you recall, Doctor Fombonne, the series of studies that you referenced in your testimony today. I was asking you questions whether those studies that focused on MMR addressed issues of thimerosal-containing vaccines. So I do want to pick up a little bit more on that thread before I resolve that line of questioning.

I'd like to direct your attention to Slide 32 from your presentation today. For the record, this would be Respondent's Trial Exhibit No. 21.

(The document referred to was marked for identification as Respondent's Exhibit No. 21 and was received in evidence.)

BY MR. POWERS:

Q As I said, right now we're going to look to Slide 32. I wanted to ask you, Doctor: In the time period that the MMR was being used in Japan, the time period that you see here on the slide, do we know anything from the data in this study about thimerosal-containing vaccines that these same children would have received?

A I have no knowledge about the other vaccines and their contents in Japan, so I cannot comment on that.

Q So, just to be clear, you don't know, one way or the other, whether there were thimerosal-containing vaccines administered to these MMR recipients?

You just don't know one way or the other?

A No, I don't know.

Q And there's nothing in the data, on the slide that you presented, that would give us information one way or the other about that question?

A Correct.

Q Now, also on Slide 32, you see there is an upswing in the prevalence rate of autism that were diagnosed in Japan in 1994, is that correct?

A Correct.

Q That was about the same time that the *DSM* for diagnostic criteria was adopted globally, is that correct?

A Not exactly.

Q Then please explain because if I recall, earlier in your testimony today, you did describe the history of diagnostic criteria and you did say that *DSM-IV* was introduced in 1994.

A Yes, I said it, and it was published in 1992. *DSM-IV* was published in 1994. However, when we were working in the field, there were *DSM* diagnostic criteria, which was widely available and used by various groups of researchers, before the finalization of this diagnostic criteria, and the publications of the books.

For instance, I can tell you that I was doing studies and using *ICD-10* criteria as early as 1989. The ADI, which is the tool that we all use, was using *ICD-10* criteria in draft form in 1989, 1992.

So the publication dates are discrete, but, in fact, the change in diagnostic criteria was implemented possibly over that period, Earlier in a research settings, and a bit later in clinical settings. It's a kind of smooth kind of --

Q That makes sense, and that gives rise to my next question, which would be: Do you know what diagnostic criteria was being used in Japan?

Let's pick the date 1991 on Slide 13. Do you know what diagnostic criteria were being used in 1991 in Japan?

A I don't know. It would probably be either *DSM-III* or *ICD-9*, probably, but it's a guess. We can return to the paper and look at the answers.

Q As you move from 1991 to 1994, would it be your expectation that in Japan they would be phasing in the use of either *DSM-IV* or *ICD-10*?

Because you jut described this progression that you're familiar with pre-publication. Do you have any reason to expect that that was going on in Japan also?

A No, I don't know what happened in Japan, and at which time. But what happens, in a given center, the change from one set of criteria to another can occur at any point in time.

So what I was thinking: It's a progressive change and shift at a national level. But in individual centers or hospitals, or research groups, there is a time where people shift to a new set of diagnostic criteria, that could be for *ICD-10*.

For instance, the *ICD-9* was used in multiple hospitals up to the late 1990s, and sometimes even in early 2000; and *ICD-10* was adopted like years after. So it happens at different times in different set-ups.

Q Right. Because I'm just trying to get to the issue here in this Slide 32 about the experience in Japan is that you have a decline, it looks like, in the MMR vaccination rates; and, then, as that bottoms out in 1992, you have a corresponding up-swing in the

prevalence of autism.

My question is: To the extent that autism prevalence is based on expanded diagnostic criteria, wouldn't it be good to know what diagnostic criteria were being used during the time of the study?

A It might be all of that, but I don't know. We need to go back to the paper to see what happened.

Q But as you sit here, you wouldn't know the answer, so we would need to go back to the paper?

A No, but I can look at it if you want. If you give me a few minutes, I will try to see what's the --

Q Sure.

A Usually, in a given study, people would not shift their diagnostic criteria when they look at trends over time except when they use hospital statistics, so let me look at it. You have to bear with me. It says on page 574 that the authors selected all children born in the catchment area between 1988 and 1996 who were diagnosed by age 7 with a progressive developmental disorder using *ICD-10* guidelines.

Q So now you think *ICD-10* guidelines, which were promulgated leading up to their publication in 1992. If you look at this graph from 1992 moving

forward in time, that's where one would see the steepest rise in prevalence, correct?

A I don't think that's correct. I think what they're saying is: Their method section is that they used *ICD-10* guidelines to diagnose children with PDD who were born between 1988 to 1996.

My understanding of what he said in the Method Section, is that they used it uniformly, *ICD-10* criteria, for all children appearing in this graph.

Q So that would then be relying retrospectively on medical records that may or may not contain the information. Sort of like a limitation of that Finland study.

When you go back in time, your attempt to apply a new diagnostic criteria is going to be limited by the record-keeping historically before that diagnostic criteria was in full use, correct?

A It depends how the medical records were maintained, which information they collected. But what matters, for such an analysis, is that you apply uniform diagnostic criteria.

If you want to assess trends, what you want to have is the same diagnostic criteria over the time span that you study.

So whether or not it's accurate that they

captured everything or not is irrelevant as long as what you do is constant and uniform over time.

Q Let's switch to Slide 50. I'm just waiting for the entire graphic to load there.

Okay. Now Slide 50, this is a graphic representation of the data study that you published in 2006, is that correct?

A Correct.

Q This is a study that looked at birth-cohort prevalence rates and looked at those prevalence rates within a Montreal school population and compared those rates over time to ethyl mercury exposure, correct?

A Correct.

Q And ethyl mercury exposure is exclusively, as I understand it from the study, derived from thimerosal-containing vaccines. That was the one source that you were assuming for purposes of the study, is that correct?

A Yes.

Q Now you described one interpretation of this study. In looking at it, a couple of things struck me. If one starts in 1987, and that's a birth year, that's a cohort born in 1987?

A Yes.

Q If you look at the prevalence rate for 1987,

you have about 45 points autistic people per 10,000. Let's round up: just 46 per 10,000, correct?

A Correct, yes.

Q At that time, the mercury exposure, via thimerosal, was 100 micrograms, correct?

A Yes.

Q Okay. If you then move forward in time to 1994, you then look and you see that the 1994 birth cohort has a prevalence rate of 98 out of 10,000, correct?

A Correct.

Q Is that correct?

A Yes, correct.

Q So that's more than doubled from 1987 if I'm not mistaken in my math.

A In which one?

Q 1994's prevalence rate is more than double 1987.

A Yes.

Q During that same period of time, the exposure to ethyl mercury via thimerosal-containing vaccines also doubled, from 100 micrograms to 200 micrograms, correct.

A Correct.

Q If I was looking at that from 1987 to 1994

and I saw a trend line of doubling of ethyl mercury exposure overlaid on a trend line of doubling autism prevalence, I might assume that there was an association between ethel mercury exposure and he prevalence rate of autism in the study.

One could conclude that from jut cutting that off at 1994, correct?

A You wold conclude that, but it would be incorrect.

Q Tell me why it would be incorrect because it's very suggestive when you look at that graphically?

A No, when you have this age of birth cohorts specifically, so it's over this period of time, what we did is: We tried to fit models to the data. There is evidence statistically what the best model which fit is a linear increase in the rates of autism.

What you see, the ups and downs, random fluctuations from birth cohort to birth cohort, they're attached to each estimate at relatively large confidence interval. Then when you look at the trend, yet there is really a linear trend, that's how the model fits the data.

There is no evidence, for instance, of an exponential return, adding to the explanatory power of

the model. So it's really over the whole period from 1987 to 1998, you have a linear increase.

As I said, in terms of the ratio for I think from each successive birth cohort, the alteration is 1.1, which suggests that it can be translated into a 10 percent annual increase in each --

Q Can I interrupt? To the extent that I understand that answer, I honestly think that it might beg the question. Because I completely understand how one imposes a linear model on a set of data, if one carries the data all the way through to end in 1998.

Of course, when you graph that, you're on an X and Y axis that has different data points than you would if you cut it off at 1994. But my question was: Why should I not assume that if you did cut it off at 1994, why wouldn't one see a positive association between a doubling of thimerosal exposure, and a doubling of the prevalence of autism?

A Because that would not support the data. You would have a linear increase. And what you have in your exposure, there is a sudden doubling of the exposure.

So you should have, in your statistical function, something which is not a linear increase over the eight years of your study. It doesn't work

what you say. It doesn't work mathematically.

I can do the same kind of data collecting, post hoc analysis that you do. We could, for instance, take the years 1987 to 1991, okay. Then you fit a trend, you have a statistical increase and there is no change in the thimerosal.

Then you take another chunk of years, you take 1992 to 1995. You have a statistical increase which is quite significant at a time when there is no change in the high level of thimerosal. So we can do that on and on and on.

If you look at this data, and look at the paper, if you look at the 1996, 1997 and 1998 years, these are years which are entirely thimerosal free. If you combine the three birth cohorts together, you calculate the prevalence rate in these three birth cohorts, it's somewhere between 75 per 10,000.

That is significantly higher from the average prevalence for the old previous birth cohorts, which were all exposed to some degree of thimerosal. So you have a very neat test of your hypothesis that, under an immunization schedule which is thimerosal free, the prevalence is higher, and significantly higher, in years when there was either a medium, or a high level of thimerosal, so that is difficult to rule

out.

Q At any point, did you look at say 1987 to 1994 and attempt to do the linear analysis and calculate a confidence interval, and a P value for that?

A No, this is not -- no, you cannot do things like that just to fit what you think that that should show. This is not the way we do studies.

So we collect the studies over that period of time, and then we model the data, we model the trend in the autism rates; and then we did further modeling trying to explain whether or not what you put in your model the amount of thimerosal contained for each birth cohort by categories, or continuously, you try to see if it explains some of the trends in autism rates.

The answer is: No. Whatever the way you look at this data, there is no association.

Q Now, another question that I have looking at this is: It seems as if there is a significant amount of variability between the prevalence rate from one birth cohort to the others, within a relatively short of amount of time.

For example, the 1992 cohort, with a prevalence of 54 out of 10,000; and then the 1994

cohort, with a prevalence of basically 98 out of 10,000. You see it if you go year-to-year.

Again, I understand how you devise a mathematical model, and you reach a beginning point and an end point, and a linear function, that describes the connection there.

But I'm just curious; What might explain this variability and prevalence rates that you see in this study?

A My guess is as good as yours. No, no --

Q But you're an epidemiologist, and it was your study.

A Yes.

Q I honestly don't know.

A No, but it's one of those situations, you know. When you select the birth cohorts -- actually, the way we count birth cohorts is somewhat imprecise, because we didn't have the date of birth. So basically, it's based on the classrooms, rather than birth cohort.

Q I'm sorry, based on what?

A Classrooms.

Q Oh, classrooms.

A We knew, you know, the grade. That's why we knew which subjects being learned. But we have

evidence that we could infer the birth cohort, based on grade. It's explained in the paper how we've done that.

So from year to year, you can have situations which could be quite substantial. If you look at that, you're right. There are fluctuations from year to year, but the trends vary.

If you look at the confidence intervals around each point estimate, and you compare to adjusted birth cohort, there would be no significant difference between, say, 1995 and 1996. It's not significant. So these are relevant situations, because they don't really differ statistically from one to the other when they are contiguous.

Q I have some more questions about the graph, but also the study that it's describing. You say in 1996, the level of thimerosal in the vaccines in this population went to zero. That's what that horizontal line represents?

A Yes.

Q How do you know that thimerosal was completely out of the pediatric vaccine supply from 1996 forward within your study population?

A Well, this data was given to me by the Department of Health of, I think it was, Montreal.

Montreal has a specific Department of Health, where there was a doctor who knows about all that, who gave me this data about the immunization schedule. I checked that myself, but that's what I was told.

Q So now the immunization, as I understand it in Canada, is something that's done by the provinces. Is that correct?

A Yes.

Q But the products themselves, the immunizations, the biological product that's being used, are those licensed by the provinces, or are those licensed by the Canadian National Government?

A I do not know that. I don't know. I know that thimerosal has been removed from most immunization programs in Canada years ago; in 1996 in Quebec. The timing of that in different provinces differ. I think in Montreal, it was removed and then put back and removed. I don't know the details.

Q Do you know the details of that in Quebec?

A Oh, well, the details of the thimerosal content are shown in the slide.

Q Again, that's based on what you were told by somebody in the Provincial Health Services?

A Yes, those are the official authorities which make the immunizations schedule, survey the

uptake of the rest of the immunization by children. It's the Department of Public Health in Montreal which does that. They are serious people.

Q Okay. I understand. The public health agency of Canada, those are serious people, also?

A I think so.

Q And the public health agency folks in Canada would be the ones who know what content of vaccines was licensed for use in Canada, including Quebec, through 1996 and beyond, correct?

A Yes, and I suspect there is someone in the Federal Government, an office, where you could find the data for all provinces. But it's actually quite difficult to find.

Q Right, and if there was data on the actual thimerosal content of vaccines from the National Government that licensed those products, if that differed from what you were reported by the Provincial Government, that might call into question the conclusions of your study, correct?

A I would have to see where the difference originated from. But I think it's pretty clear that in Quebec, vaccinations have been thimerosal-free since at least 10 years, and it's very clear. There have been all sort of indicators that the rates of

autism have increased and that this increase bears no relationship with thimerosal.

Actually, I am doing another study of that kind to just replicate because people asked me to do these studies. So we will have soon have data replicating these same findings in a more recent period of time. From what I've seen so far, the rates are as high as at the end of this period; again, in the thimerosal-free environment.

Q When do you anticipate publication of that?

A Not soon.

Q I mean, like months or a year? I'm just curious.

A In a year, probably.

Q Okay. So then another question I have for you is shifting subjects a little bit, but still related to this study.

MR. MATANOSKI: On these subjects, I want to be clear that your question about licensure was about licensure, and not about use of vaccine, correct?

MR. POWERS: It's about licensure, yes.

MR. MATANOSKI: Okay.

MR. POWERS: Well, it's about licensure, and then to the extent that licensure reflects what is actually in use.

BY MR. POWERS:

Q So another question I have is, the children that you're tracking for the prevalence rate here, these are children that went to a particular school district. I think it's a school board in Montreal. I think here, it's a school district. Is that correct?

A Yes, yes, and there's more, because the school boards are organized by language in Montreal. Before it was religion. Now it's language. So you could have in the same geographical area, a school which belongs to one school board in the next school building. So you have a school board based on language differences.

Q Yes, we tend to do it geographically.

A Yes, but it's more or less, a school board which is covering the whole western part of the Island of Montreal, which is a rather wealthy, affluent part of the city and, therefore, we see that.

Q Exactly, and so it's that population that we see the red line and the squares tracking the prevalence rates, correct?

A Yes, correct.

Q Now my understanding is that you then were looking at vaccine coverage rates, also.

A Yes.

Q Or uptake rates -- I've heard those terms used interchangeably. But basically, it means how many people within your study population are actually being exposed to the vaccine. Now your update group or your exposure group, was that group of children from the exact same geographic location in Montreal that your prevalence data comes from?

A No.

A Where was it from?

Q It was from Quebec City. There was a group there, which is called the National -- something. It's a public health organization in Quebec City, which conducts repeated surveys amongst children that are, I think, four or five years old, which allows them to calculate regularly. So if you have to do that to calculate which is the proportion in that population, which is currently vaccinated, according the full immunization schedule.

So the proportion of MMR coverage, which I used on the previous slide, is derived from this particular study. So the trend for MMRUs is originating from a different area, because there is no data on this particular area, that we could map them directly to the roots.

There are some other studies that could have

been used in Montreal, which are functional surveys. But in terms of estimating a trend with regular surveys, which I don't know the same methods, there is only settled data.

THE WITNESS: So I want to make sure that I'm clear. Because when I was looking at this, I was assuming, and it sounds like I was incorrect -- I was assuming that the prevalence rate that you're tracking within a population is within the same population that the exposure information comes from.

But that isn't correct here. These are from two different places geographically, what, 250 kilometers apart; Quebec City and Montreal.

A How much?

Q I'm guessing 250 kilometers?

A I think you're correct.

Q So we have a prevalence population that is a physically different population than the exposure population, correct?

A Yes, but we had data from the local area where the study was done. Yet you could say, these are ecological aggregated data. So it would still leave open the question as to whether or not children with autism were actually exposed to this medication.

So that's the limitation of all ecological

analysis. Often people use what they can to estimate trends, and this is the best information that we have to look at trends in immunizations in Quebec; extrapolating from the Quebec City repeated surveys to the whole of the population. That has some pitfalls, but it's also the best data that we could obtain.

Incidently, the downhill trend in MMR coverage is probably rightly estimated. Because there has now been a measles outbreak recently in Montreal for the last three weeks. So clearly, it has gone down in recent years.

Q Now you mentioned that data aggregation and looking at analogous data on exposure is the best information that you had in this instance.

So when I hear that, it makes me believe that for the physical Montreal cohort, what you're saying is that their actual exposure data does not exist, and you therefore had to use exposure data from Quebec and aggregate it province-wide to come up with your best estimate for the Montreal exposure. Am I understanding that?

A That's the design of the study. It's ecological and that's what it is. Yes, you're absolutely correct. That's what we did.

Q But it would be better data to use, if

Montreal data existed, so you had the actual exposure rates for the actual children whose outcomes you're tracking. Let me finish. That would be better than aggregate data from another city, 250 kilometers away. Is that a fair statement?

A Not necessarily, sir -- there are factors which influence vaccinations which are, in particular, social class or the proportion of immigrants in a particular area.

This area, the western part of Montreal, is very stable. It's a very wealthy population. It's an Anglophone population. Our hospital, the Children's Hospital of McGill, does prevail in performing this function for this population for care.

I can tell you from all the studies which I have done, where we had actually in my autism service, data that individual vaccination records, of children with ASDs, included in other studies, where the uptake of vaccinations was 100 percent or 99 percent.

Q And I totally understand the update; that there might be a grade in uptake rates.

A What I mean is, I'm conceding that the children who have PDDs in those studies; where we didn't have individual immunization records, because that's a limitation of the study, we're very lucky to

have followed the official immunization schedule, because of the nature of the population from which they arise.

Then the Quebec City data, in terms of vaccine intake, coming from sort of a rather affluent area; so middle class, or lower middle class. So it's probably not a bad trend to use to apply to our Western part of the island.

If you were to take Montreal data from autism in that particular study, in the East part, it would tape into very impoverished populations, or areas where there are large proportions of immigrants, where vaccine outtakes would be very different and not peculiar to our particular situation.

Q Right, and I understand the difference between uptake rates from one location to the other. But the difference that you're looking at here, given an uptake rate, is what your prevalence outcome is.

So even though your uptake rates might vary geographically based on the social-economic factors, within a population where you define the uptake, any association with the outcome should be consistent. I mean, it's not as if people are going to have different prevalence rates, based on where they live. Once you've got the accurate data on uptake, it

should make a different -- the socioeconomic, and sort of participation bias factors, right?

A I'm not entirely following your argument.

Q I didn't mean to make it an argument. I meant to make it a question.

A No, no, no.

Q So let me rephrase it for you then. I understand that there are reasons why, from one physical location to another, the uptake rate or the vaccine coverage rate, might be different. I completely understand that.

But within a population, those socioeconomic and other factors shouldn't make a difference, given the update in that population and prevalence. That relationship should hold constant across any population, correct?

A I think you use "population" in a different sense. Are you talking about "sample"?

Q Sample, sample.

A Okay. That's different. So your point is to say, in a given sample, if you have on that sample, on that preparation from which a sample has been selected, if you know what is the uptake in terms of various immunizations, yes, you could apply it.

Q Okay.

A Yes, of course.

Q Okay.

A Can I say something in relation to what we were discussing?

Q Is it in response to a question of mine?

A One of your questions.

SPECIAL MASTER HASTINGS: I think, Doctor, it turned out, when you understood that question, it was very simple and obvious; yes, of course.

THE WITNESS: Okay.

MR. MATANOSKI: I'm not sure that he did understand the question, because he answered uptake versus prevalence. He answered uptake. If you look at the sample, yes, and I'll know what the update is in the sample. But I think the question went to prevalence, and why not use prevalence in the same sample?

SPECIAL MASTER HASTINGS: Okay. My point was simply going to be, sometimes we lawyers ask questions, Doctor, that you're maybe looking for more to it than there is. Sometimes, we're just trying to confirm. We summarized what you just said in a short way, to make sure we're under-

standing it; and sometimes, it's a simple yes, you know.

THE WITNESS: Okay.

SPECIAL MASTER HASTINGS: So don't read too much into the question. We may, you know, get done a little earlier.

THE WITNESS: Okay.

BY MR. POWERS:

Q And indicating that that was, in fact, the case, I'm going to move on to another discussion here. Just a question I had, and we can pull this slide down. I don't have any more questions about that slide or any others immediately here.

Are you aware of any epidemiology that explored a potential association between regressive autism as an outcome, and a combined thimerosal MMR exposure?

A No, I don't think that has been looked at, in as specific a way that you mentioned. There is data which contests this hypothesis.

Q I understand that, and I'm trying to keep it to the very specific published studies. I take it from your answer there, although there may be data out there that somebody might want to do a study on, as of right now the answer would be no.

A I think in terms of published studies, I don't think there is any study which is linked the

combination of the two exposures in relation to regressive autism. But we can use of the existing data to make sense of this question.

Q Then the next question is, are you aware of any published epidemiology that explored an association between regressive autism and the MMR, aside from any thimerosal-containing vaccines considered in the NEX?

A Yes.

Q And what study would that be?

A Between regressive autism and MMR?

Q Right.

A Well, all the studies have been presented this morning.

Q We talked about a number of those. Would it also include your 2001 study?

A Yes, there will be one study; the study by Taylor in 1999 in the U.K. gives a lot of data on regression and MMR exposure. Two Japanese studies provide some data on that.

Q And looking specifically at the regressive presentation?

A Yes, and no study was positive.

Q I'm sorry?

A No study showed an association between an

MMR exposure and regressive autism.

Q Correct, and are you familiar with the Cochran Collaboration?

A Yes.

Q I'm sure that you're aware that they did a review article in 2005, that looked at the studies, and sort of did a review of epidemiology on studies examining vaccines and measles, mumps, and rubella. Are you aware of that review?

Q Yes.

A Are you aware, in that review, that they describe your study as having a number of possible bias in the study; and that number was so high that interpretation of the results was difficult. Do you recall if that was their description?

Q Yes, and I would like to comment on what they actually said, because this is cited out of context. The preceding paragraph, I think, describes the studies, the design, the findings; and then there is a sentence, which is completely unsubstantiated.

There are no comments about what rules, what virus, we actually refer to. It's very hard to actually pinpoint what they actually mean by that; and they comment on all our studies with the bias, the instant review, which is, how should I say, naive.

I said in some words, you can say, for each study, that there are bias and issues. That's fine. But what is less acceptable? I think, as you saw, it's flawed or is biased, without giving me any substance.

Just to follow-up on that, because I know this particular sentence, because it has been used on the web by those people, so I know it. It doesn't impress me.

I can tell you, the study, which was published in 2001, has been widely quoted. If you look at the study done by the NIH-funded investigators from the U.S. recently, looking precisely at the regressive phenotype and the Wakefield phenotype, they actually set up to do the study to follow-up on my own initial study, to try to replicate the findings; and they were quite complimentary about that study.

Q I knew you would take issue with it. But I just wanted to hear your comments on it, because I had run across that.

So I want to shift gears. We've been talking a lot about MMR, and we talked a little bit about some of the studies that you mentioned in your presentation today, in your report and in your direct testimony, on the thimerosal issue.

There is one, the Verstraeten Study. That was the article published in 2003 in Pediatrics, and Thomas Verstraeten is the lead author. You're familiar with that article, I assume?

A Yes.

Q One of the things that struck me, and I just want to get your comments on this -- what struck me is that if one looks at that study, and looks at the number of actual cases of autism that were identified in that study population, one comes with a prevalence rate of roughly 20 per 10,000.

You'll recall, one HMO had something like 202. I mean, we can put the numbers up. But if you recall as correctly as I do, it's roughly 20 out of 10,000. Does that sound about right?

A That is true.

Q Well, overall, with the three HMOs, if you looked at the total number of kids, your denominator, and looked at the total number of "Ns" which is the numerator they're looking for with autistic diagnosis, it would be roughly 20 out of 10,000. Does that sound about right?

A I would have to check. But if you've done that, you're falling in the same trap that you described this morning within the CDC. Because you

would be pulling together the definition of where the problem is.

Q But you're anticipating questions that aren't coming, because I actually disagree with you on some of these things.

A Okay.

Q That's why I want to explore your opinion. So let me ask the questions, and we'll save some time. So the question is a simple one. Do you recall 20 out of 10,000 being roughly the prevalence rate?

A No, I'll have to look at the paper.

SPECIAL MASTER HASTINGS: Well, he'll give you the paper, if you want to look at it.

THE WITNESS: I recall there were 202 children with autism HMO B, 20 which are not --

SPECIAL MASTER HASTINGS: Again, the question was, do you recall. You said no. You've answered the question.

THE WITNESS: Okay.

BY MR. POWERS:

Q And since you don't recall, we're going to show you the paper --

A Okay.

Q -- and we can just cut to it. Okay. Well, thanks to Mr. Shoemaker, we have the paper up. I know

this is an exhibit. So this is Petitioner's Exhibit 150.

SPECIAL MASTER HASTINGS: No, I think it's Respondent's Exhibit P, at Tab 150.

BY MR. POWERS:

Q Okay. So let's look at page 1043.

A Yes.

Q We want to look at the number of cases of autism that are present. If you look at HMO A on this table, down at the bottom, you have autism. You have autism that occurs at the column on the left under HG. Those are the ranges of exposures.

But basically, they're looking at two different ranges there. So you have a total number of autistic cases in HMO A of 20. Is that right; twelve and eight?

A Twenty-one.

Q No, it would be twenty; twelve and eight.

A What about the one?

Q Oh, and then the one, yes. I'm sorry, so twenty-one. Yes, I know, number one is ADD. So we're just looking at autism, which were the last two.

MR. MATANOSKI: No, it's autism 0275, 87 through 162.

MR. POWERS: So it's twenty-one.

BY MR. POWERS:

Q Then if you look over at HMO B, you've got 37, 148, and 17. That's 192? So that would be the numerator. Then the total number of children in each of those HMOs would be the denominator.

If you look at the text, and that's why I'm trying to find it in the text, you would have in HMO B the total number of children that are included in HMO B. That would be on page 1031. Do you see the boxes?

Then at the very bottom, it says, "Final Cohort." For HMO B, you've got a Final Cohort of 110,833 children, and we know that you had 192 autistic diagnosed children in that cohort, correct? That's the number we already figured from the other page.

A It's not on mine. I have more than you.

SPECIAL MASTER HASTINGS: I think you may have been wrong in your addition. I've got 202,000.

MR. POWERS: You know, that's what I had before; yes, 202.

THE WITNESS: It's 202,021.

BY MR. POWERS:

Q That actually makes the math somewhat easy. Because actually, 21 out of 13,000 would actually be a little bit less than 20 out of 10,000, in HMO, right?

A Yes.

Q And 202 out of 110,000 would be roughly 20 out of 10,000 in HMO B, correct?

A Yes.

Q So that math exercise is just to get to the point that if you look at the population here, you are looking at a prevalence rate of roughly 20 out of 10,000.

Now my understanding from your earlier testimony is that you would expect an actual prevalence rate more on the line of 60 out of 10,000. Is that correct? That's typically what you would expect to see in a population; 60 out of 10,000?

A Yes, those are recent estimates, yes.

Q So in this study, it appears fair to say that there's an under-counting of autistic children in this sample, correct?

A No, I can't say that unless I know exactly what they did in terms of subject selections. It depends. It's a curiosity, as I recall. So the number of cases identified would be closely tied to the length of observation in the population. So that could reflect that, and just that.

Q And the numbers could be lower than what one might expect, based on your general prevalence

estimates, because it's automated dated generation. It's not case ascertainment.

A Yes.

Q It doesn't take into account diagnostic substitution, and all of the things that you talked about before that might drive that number up, correct?

A Yes, but the goal of the study is not to assess prevalence.

Q I understand. I understand. But that wasn't the question. I just want to make sure that we're looking at the same numbers and talking about the same thing here.

Now also, if you look at the text of the study, you might remember that the average age of diagnosis is 44 to 49 months. Is that an average of diagnosis for autism that you find in your experience?

A It's very consistent for studies done for children born, I suppose, in the mid-1990s. That would not be unreasonable. That would be just below age four. In recent studies we've done in the U.K., the age of diagnosis was, on average, 36 months.

Q That's the number that I was remembering. But that's based on criteria methodology that you're using now, as opposed to what was being used 10 years ago?

A Yes, I mean, this is not really inconsistent with many other center's experience.

Q This study, it purports to look at a relationship between thimerosal exposure and adverse and neurological outcomes, particularly ones that are identified by *ICD* code, correct?

A Correct.

Q And in this study, the study design required that at least 50 cases of autism be identified within one of the HMOs for any statistical analysis to be done relating it to vaccine exposure, correct?

A Correct.

Q Out of the three HMOs that were used, only one of those HMOs had a number "N" of autism diagnosed children large enough to do an associational assessment with thimerosal exposure, correct?

A I'm understanding whether they used two HMOs first as training to make that association between TCVs and various outcomes. So they used A and B. They couldn't find enough cases in A, which was therefore an informity for the autism analysis. They had enough cases in B, 202, to make the relationship and found no association.

Therefore, when they went to HMO C, they didn't really pursue that, because it was not a

positive association in B.

Q Well, actually, with HMO C, they selected an HMO with a population that was several times lower than the population in HMO B. That's what you see that just got blown up on the screen there.

So when they added C, again, you add another HMO, where your end value; that is, the number of autistic children, doesn't reach the level 50 that you would need to associate with the vaccine exposures, correct?

A I just need five minutes to look at this.

My understanding of their design is that they used HMOs A and B as a first pass, and they were aiming at using HMO C as an independent sample to confirm association which had been found in HMO A and B.

So as far as autism is concerned, HMO A was not even analyzed because there were too few cases, which is logical and was in line with that analytic strategy. In HMO B, there was no association between autism and thimerosal containing vaccines. Therefore, this association was not even pursued, because there was no attempt for concern for something which was not even there.

Q Do you have any idea, given the size of

these cohorts in each of the HMOs, 110,000, 16,000, 13,000 -- I mean, we're looking at -- and I hope I'll not make another math error here -- close to 140,000 children in there.

A Yes.

Q You would expect that, given a rate of 60 per 10,000, you would have many hundreds of autistic children that would be captured in this study, correct? That would be your expectation, based on what you think the actual prevalence rate in populations at this time was?

A No, I would not expect that in such a dead asset --

Q In such a what?

A In such a dead asset that you would have as many showing that you would predict, based on population surveys. Population surveys are different types of studies. They are aiming and estimating the magnitude of the problem, the prevalence. They have their own method, as they come with figures to estimate these numbers.

This is a data base or data set, which is available to do research. But we know that all existing dead assets have recording problems. You would not use the VSD database to estimate problems.

So if your question is, does that lower problems in the VSD study indicating work flow, no. It's something that you would predict.

In addition, for their purpose, which was to look at whether or not exposure to TCV increased the risk of autism, you know, whether or not they captured 100 percent of the cases of the preparation or just 20 percent was irrelevant, as long as there is no differential selection bias; meaning by that, that you assume that you cannot reasonably expect that children who are in these studies are representative of the pool of autism cases in the population, which is the target population.

Therefore, the odds of exposure to TCVs in these autism cases, even though it might not be the full autism case studies, is probably equal to represent what is happening in their home population of autism subjects. Therefore, there is no bias.

Q Yes, so completely aside from bias though, it's not irrelevant how many autistic subjects you capture. Because having a larger end is going to give you more power. It's going to give you more to work with, when you're looking at effects. I mean, that's true, isn't it?

A That's true. A larger sample size would

give you more precision to estimate any types of association.

Q Right.

A In that case, there is no association. So even with a larger end with autism, they would have no association.

Q But that's circular.

A No.

Q Now that's the post-hoc reason that you're making the conclusion that given a small end relative to the size of the population, and a small end compared to what you think really would exist in there, the 60 out of 10,000 -- if you had that higher end, you would have more precision. You've already said that.

But you're saying in a circular way, aren't you, that you don't have to do that, because you know ahead of time that there's no association? That seems circular.

A I certainly didn't say that. I think you don't understand the difference between a status decor power sample side on the one hand, and estimate of associations in an epidemiological study.

When we do a study like that, what we look at is the point estimate of the association, the

relative risk, the other issues. That's the measure of association. That's what matters.

If it's close to one on a small sample or a medium sample, it's unlikely that you have missed a very strong association which would be there in the nature, okay? Maybe 1.2. It could be 0.8. But if it's close to 1, it's likely that there is not much association.

The sample size comes in in augmenting the precision of your estimate of association. So instead of having 1.0 with a confidence interval ranging from 0.6 to 1.9, if you double the sample size, you would have still 1.0 because there is no association. But you have a confidence internal of 0.8 to 1.4. So that's what you gain with incremental samples. You increase position. You reduce the confidence limit of your estimate.

But what matters, in terms of association or assessing if there is bias or not, is looking at the point estimate, which is the value of the relative risk or the value of the other issue. That's what all counts.

Q Yes, and I understand the concept of odds ratios and confidence intervals. But particularly in a study like this where exposures are stratified, you

do not have a zero group. Because remember, this study is looking at the differences in outcomes, based on the smaller versus larger exposures.

So when you have these exposures that happen at 25 microgram intervals in real life via immunization, you take away the zero exposure. You stratify by grouping these together. If you had more ends to work with, you could break that stratification out some more, couldn't you? You would have more ends to look at, to compare against exposure levels, and that might give you more information.

A Could you be more specific about what you mean? Because it's not entirely clear. If you have more ends, you could do what.

Q If you had a study that had generated more autism cases, more ends, and then we're looking for effects, there would be more. There's a possibility, with that bigger end, that you would be able to get more dose-specific associations, assuming that they existed at all?

A No, no, that's not the way it works. You would have more, assuming that the autism cases which are in that study have been randomly selected to represent the pool of autism cases which were available should agree with this population. Then by

adding more cases of autism, you would not change the trend of the level of association. There would be still no association. There would be just more precision in how the lack of association shows. It would not affect that.

Because this study, in any series of cases, 200 cases gives you a relatively high number. If they are well chosen, there is no systematic bias in the selection of these cases. These cases represent the distribution of exposure in the autism population. Therefore, you can estimate association on different levels of exposure, and you would not gain much. You would just gain increasing position by adding more cases. It would change.

Just to make it clear, it would only change if you had selected children in the first phase and first phase, which would be systematically different from those which would be left out, and there is no evidence of that.

Q Yes, so selection bias, it's not disparaging. It's not nefarious. You know, you're trying bias against somebody. It's a technical term, right, selection bias?

A Yes, sure, yes, it would be that participation

in the study is actually related to the experience status.

Q Right, and then certainly, any exclusion criteria that were applied to potential members of the cohort, exclusion criteria is going to affect ultimately the outcome of your study, correct?

A Yes, that would be one way by which some bias could occur. Also, it's a way to control bias.

Q Right, and it could cut both ways.

A Sure.

Q I mean, bias could be introduced or bias can be controlled for, and applying exclusionary criteria is one way to do that.

A Yes, I agree.

Q Now this study I have seen cited for the proposition, that it is a negative study, that it disproves a causal connection between thimerosal-containing vaccine and autistic and other neurological outcomes. Have you seen the study portrayed that way, as a negative epidemiology?

A Yes, I think most institutes or committees who have reviewed the study have found it to be a negative study.

Q And you're aware that the author of the study, Dr. Verstraeten, has somewhat of a different

opinion about whether it's a negative study, from what you just described? I'm just curious, do you know Dr. Verstraeten? Have you ever met him?

A Not at all.

Q Have you ever talked to him about this study over the phone or anything?

A Never, never.

Q Okay. Are you familiar with a Letter to the Editor of the *Journal of Pediatrics* that Dr. Verstraeten wrote in 2004?

A I think I've read it, but I forgot.

Q I'm sorry, you read it?

A I read it, but I will need to read it again, if it's important.

Q Well, I think it is important on this issue of, is it a negative study or not. We'll see if we can pull it up here.

SPECIAL MASTER HASTINGS: There is a copy of it in the record already, isn't there? Does anybody have the citation for the record handy?

MR. POWERS: At the motion to compel hearing, Petitioner said it would have been Petitioner's Exhibit 21.

SPECIAL MASTER HASTINGS: All right. But it's not in the record of this Cedillo case?

MR. POWERS: We do have copies, if you want it filed here in this case.

BY MR. POWERS:

Q Since we're obviously having trouble getting it up electronically, Doctor, I've got a copy of it for you here.

A Okay.

Q We can leaf through it a little bit.

A Thank you.

SPECIAL MASTER HASTINGS: All right. so we'll make this Petitioner's Trial Exhibit 16.

(The document referred to was marked for identification as Petitioner's Trial Exhibit No. 16 and was received in evidence.)

BY MR. POWERS:

Q Doctor, it looks like you're doing it, but I was going to ask you, take a moment to read that. Then if you could just look up when you're done, I'll just have a couple of questions.

A You want me to read everything?

Q I think it's pretty short, if you just want to read that, or just have it refresh your memory. I just have a couple of quick questions.

A Yes, okay.

Q Okay. So again, this is for people who don't have it in front of them. It's a one page Letter to the Editor of Pediatrics that Dr. Verstraeten wrote. He wrote this in Belgium, where we was working for Glaxo, after having his two year fellowship at the CDC.

In this article, at the top of the second column, he expresses surprises that his study is being interpreted now. His words are, "Surprisingly, however, the study is being interpreted now as negative by many, including the anti-vaccine lobbyists."

He goes on to say, "The article does not state that we found evidence against an association, as a negative study would. It does state, on the contrary, that additional study is recommended, which is the conclusion to which a neutral study must come." Do you see where I'm reading?

A Yes.

Q So it would be fair to say that the author of the study has a different opinion about whether it's negative than what you were just reporting your understanding to be, correct?

A Yes.

Q The author of this study describes it as a neutral study that warrants further study.

A Yes.

Q In fact, as I understand, the CDC -- and if you don't know, you can tell me -- the CDC, as I understand it, has initiated, triggered in large by Dr. Verstraeten's study in 2003, at least two case control studies; one looking at thimerosal exposure in neurological outcomes, and another looking at thimerosal exposure in autism, particularly. Are you familiar with that work?

A I've heard about the case control studies. I don't even know at which stage it is, if it's done or not. But I know there is ongoing work on that.

Q Okay. And I was just trying to find out from you, have you participated in the design of those studies?

A No.

Q Do you anticipate sitting on a peer review panel for any journal that might be looking at those studies?

A That's likely to be the case, yes.

Q Do you have any idea of what journal you might be sitting on that would review?

A As a reviewer.

Q Yes.

A I review for so many journals. You know, it's the kind of study which might likely come to me as a reviewer, but I don't know.

Q But there's nothing coming your way right now, is that correct, on either of these case control studies?

A No, no.

Q Okay. And as I said, I just had a couple of questions on that letter, but I did want to discuss it with you.

So, Dr. Fombonne, in hearing your testimony and looking at the charts and the graphs that you presented, the impression I'm left with is that any reports of an increased incidence of autism in the population, you believe to be an artifact, so to speak, of better case ascertainment, wider diagnosis, expanded diagnostic criteria, all of those things that you've described in detail. Is that a fair summary?

A Again, let me say that I believe, just for the sake of believing. I'm open to see what the evidence shows. I think when you see trends of either direction, you have a duty before you interpret them as signaling a change in the incidence of this order, to rule out alternative explanations, as well I've

been trying to do.

When you do that, in all published studies, be they prevalence studies or incident studies, none of the existing data can be interpreted as positively showing an increased incidence, controlling for other factors.

Because most of these do not control for factors changing, and the current view of many, many people is that unless we can generate new studies, looking at the incidents over time in ways with designs which adjust for change in case definition and settlement, we won't be able to address this question from existing data.

Q And maybe to put a finer point on it, I have the impression that whenever there has been an allegation of either the MMR or thimerosal-containing vaccines, the introduction of those or the increased use of those, whenever there is an allegation that that is leading to a rise in the incidents of autism, your response is generally that it doesn't. Because any rise that you see out there is, again, the artifact of the expanded diagnosis and case ascertainment, and diagnostic substitution, correct?

A It's not completely that. I mean, the claims of the rising resolution have been made in the

context of this vaccination hypothesis. So the effect is like, as we discussed, changing diagnosis systems. So how you decide what is a scientific question which requires empirical testing of competing models to explain the same observational data.

So far, there is no data which is convincing, which can really rule out alternative explanations, as I said before. In fact, it's not only looking at the rise. Because when we have like a discontinuation in exposure to particular vaccinations, you can still see the rise going on.

So it's quite convincing in some ways, that a lot of these files, if not all of it, has nothing to do with vaccination. Otherwise, when in the country, TCVs are discontinued or immunizations are discontinued, you wouldn't see the rates of autism continue in their trend up.

Q I think that when you're just talking about hits on something that, to me, it sounds almost like trying to have it both ways. If there is an allegation that you have a rise that is caused by or is associated with exposures like thimerosal or the MMR, the rise is explained away by diagnostic artifact.

But when you fail to see a drop in rates

after the exposure is removed, you say, well, that's proof that the exposure wasn't causing anything.

Well, really, you would expect to see, because of the diagnostic substitution, case ascertainment, wider diagnosis, earlier diagnosis, more attention, all of that, you would expect to see prevalence rates continue to rise. So it just seems like those are trying to have it both ways, doesn't it?

A No, because you are using a type of analysis which is basically ecological in your reasoning. You are trying to compare trends and rates of a predominance of autism, with trends in exposure data. This is ecological reasoning.

There is a large body of evidence, both for MMR and TCVs, which is not relying on ecological data, where prevalence is not an issue. Epidemic is not an issue. You look at cohort studies. You have to expose them.

Q I'm sorry, what studies?

A Cohort studies or case control studies, so you know what is the disease status on the child. You know what are the exposure status, and there is a body of data which is replicated across that assets, across countries, showing that exposure of particular

children to either MMR or TCV vaccines does not increase the risk of autism.

This is done in studies where, again, the issue of prevalence, et cetera, is absolutely irrelevant, okay? So this body of data is there, and the ecological studies just confirm what has been found in case control studies. So I think it's pretty convincing, if you look as I do, at replication of findings of cross studies as my main to learn about the nature.

Q The case control studies that you're talking about, the MMR case control studies, were the ones that we've talked about during your testimony today, that didn't include U.S. populations with TCV and MMR exposure. So there aren't any case control studies on that issue, which is the issue here. Am I correct? I mean, we've already talked about. I think we have.

A No, I think actually there is more data on this issue that maybe we have discussed. Actually, when I was reviewing my slides at the lunch break -- and if I can maybe show you the slide I used this morning. If it's correct, it's the slide of Madsen, for instance.

MR. POWERS: So just a quick thing, are we now introducing new thing?

SPECIAL MASTER HASTINGS: He wants to look at his same slide.

MR. POWERS: Oh, same slide, I'm sorry.

THE WITNESS: Same slide, yes -- so from this morning?

SPECIAL MASTER HASTINGS: Is that the right slide?

THE WITNESS: Yes, this is the right slide.

SPECIAL MASTER HASTINGS: It's Slide 427.

THE WITNESS: Slide 427 -- as we discussed, this study by Hviid, which I presented this morning, shows on the bottle the actual amount of thimerosal which is contained in the vaccines in Denmark. I think you mentioned, at one point, that it was 75 micrograms of thimerosal which, in fact, it is 125 microgram of mercury, which was contained in Danish vaccines.

So that is important, because when we discuss the Madsen Table 2 findings, where we had data on the joint exposure to MMR and thimerosal continental vaccine, there was a time in 1991 and 1992 where, in fact, children were exposed to that level of ethyl mercury and MMR, and that showed no increased incidents, as we discussed this morning. Incidently, this level of exposure is quite comparable to what

Michelle Cedillo received. That's one thing.

The second thing I would like to show is that, again, the slide I used this morning, which Slide Number 50, and I know we just reviewed it --

Q That was your Montreal study.

A Yes, you will recall that the slide doesn't show the optic rate of MMR during that study. But the rate of optic was quite high. Probably during the periods like 1992, 1993, 1994, 1995, it was somewhere between 93 to 94 percent of MMR uptake. Again, for this population, in particular, the uptake is likely to be 100 percent.

So during that particular segment of this ecological study, you have high exposure to ethyl mercury, 200 micrograms, and exposure to MMR, okay? Yet, when it's constant, you see the rates are climbing up.

Q For case control studies in the United States looking at thimerosal-containing vaccines, those are the ones we are awaiting from the CDC, correct? We talked about those a minute ago.

A I'm sorry, could you repeat?

Q On case control studies, looking strictly at thimerosal-containing vaccines, apart from the MMR, in the U.S., we just talked about the CDC ones. But

those are the only two that are in the works, as far as you know. Is that correct; or do you know of others? I don't want to foreclose that.

A There are a number of investigators now currently collecting data, like large case control studies and population-based samples, where they collected a lot of data, but on environmental factors. Also, everybody collects immunization records. Many people have that. So there will be some data available. But I don't know of any study which prime goal is to investigate that, besides the CDC study.

Q I was puzzling over Slide 47. When it was up there, it wasn't making sense to me. Now I see why it might not. Let's get back to Slide 47, if we could. We're looking at these doses: one dose, 25 micrograms; two doses, 75 micrograms. I mean, my understanding is that each dose had 25 micrograms.

A No, it's 50 micrograms at five weeks; 100 micrograms at nine weeks; and 100 micrograms at 10 months. This is the amount of thimerosal. The total is therefore 250 for thimerosal, which translates into 125 micrograms of ethyl mercury, an exposure which is that of Michelle Cedillo.

Q So for each successive dose, they use more thimerosal than the successive -- it just still

doesn't add up. If it's 25 micrograms of ethyl mercury per dose --

A No, it's half of the content of thimerosal, okay, and you have three doses; one who has 50 micrograms of thimerosal, then 100 micrograms of thimerosal, and then again 100 micrograms. So that is 25 plus 50 plus 50 of ethyl mercury.

Q And you're sure that's what the actual content is on the vaccine?

A I actually looked because I was surprised that they let that go. But I looked at the Madsen study and the MMR of the Hviid study. Actually, it was written like that, too. It's not a mistake.

Q Now a few more things just to I think get us to a point where we can wrap up here. Are you familiar with any population studies that look at industrial emissions as potentially associated with adverse neurological outcomes?

A You mean currently or published studies?

Q That have been published in say the last say couple of years. And again, not a trick question. I just want to know. I think one was in Texas, the Palmer study, and there was another one, Windham I think was the lead author's name in the Bay area. Are you familiar with those studies?

A Yes, I recall the Palmer study, yes.

Q And the hypothesis in those studies and what those studies found was that in areas where you have high exposures due to industrial emissions including elemental mercury at least, there were initial findings of a higher rate of neurological disorders in those children as compared to people outside the exposure area. Is that a fair statement?

A Yes. There was some correlation between autism rates assessed through special educational ascertainment and indices of mercury in the atmosphere. But can I say something about that? But what they did, they collected data on children with autism in I think it's 2001, the study. Let's say that. They collect data on children who were recorded in the special educational system with an autism category in 2001 so they are aged six to 11 say.

Then they correlate that with a rate of mercury in 2001. It makes no sense because you don't correlate the rate of mercury in 2001 to explain a disorder which occurred four, five, six years ago. The specification of the model is completely wrong in that study, and that showed that their statistics are spurious.

Q So your opinion would be that those studies

are uninformative?

A No. No, I think it could be informative, but that particular study is completely not well designed for the reason I just indicated. Unless they look at reverse causation.

Q Given what I understand from your testimony, that prevalence rates in the U.S. population are roughly the same today as they were say 20 years ago, is that fair? Actually, I should correct that. I used the wrong word.

The actual incidence of autism in the United States, that is the percentage of people in the population who are autistic, is relatively the same now as it was say 20 years ago. Correct?

A We can assume that.

Q I'm not asking about prevalence rates and inflation, but just the actual, what you believe to be the real incident rate has basically been static over the last 20 years.

A Yes, a starting assumption, yes.

Q Assuming that, and I didn't even attempt to work up the numbers, and I just don't know whether you have but I'm curious. Based on that analysis, how many autistic adults, that is say over the age of 18, how many autistic adults should we be seeing in the

U.S. population? Do you have an estimate?

A In numbers? I don't know. I have not made a calculation, but it's easy to do if you want. You need to account for the fact that there might be some increase in mortality rates when the studies show that the standardized mortality ratio in autism is increased, so there is more mortality than the other groups so you have to account for a few things of that kind.

Q And again, I was just trying to get an idea if you had a number, because I'm curious as to how many autistic adults we ought to be encountering in the U.S. population if the true incidences remain the same historically. You don't have that number, but you think it can be calculated I assume just by using the 60 out of 10,000 and morality within that.

A Well, yes. Probably with an attenuation factor of that kind, so I don't know which kind of rate I would apply, but yes, you could do these calculations.

The calculations that we provide are based on empirical studies. The point in terms of adults is that there has been no survey of autism spectrum conditions in the adult population. That's something which remains to be done. Unless it is done,

speculations will go widely, you know?

Q Right. In any direction. I mean, if you don't know, people can speculate and hypothesize and make all sorts of assumptions without facts, correct?

A Of course. Yes.

Q Just very quickly here, you've testified as an epidemiologist today. We've talked about some underlying causation issues. But so much of what you've been talking about is related to diagnoses. I was curious how many autistic children you actually treat as a physician.

A Currently you mean?

Q Yes, a ballpark number.

A My caseload is probably like 200, 250 a year. I don't know. I have ongoing patients who come back and forth. I assess probably these days about 150 new cases a year, maybe a bit more than that. I see kids for psychopharmacology clinics, I see a number of them which come back regularly for treatment and management.

Q And for the 150 children that you assess each year, again without burning a huge amount of time, can you just give me a quick description of how you assess them? If you could just run through a list of how you would assess those 150 children that you

see?

A It really varies. We use, the standard technique that we use usually is to use an autism diagnostic interview which is a developmental interview with the parents. That lasts three hours. We then have the child coming back with his parents. We do then a neurological examination. We do in different days a speech and language assessment, a cognitive assessment, occupational therapy assessment. We do the regular medical exam, family history and everything. I usually do an ADOS with the children which is a direct examination. So that's the full, complete assessment.

The one we use for cases which are more complex, that would be typically children who have some language skills, which are not mentally retarded, or children who are included in research studies where we want to do the full phenotypic assessment.

On the other hand, because of pressure on our time and on our waiting list, I do sometimes see children within about two hours. When the case is not complex I can do a relatively good job of assessing a new child, completing my diagnostic evaluation in that timeframe, but I always see the child again, have a follow-up. So that varies. It will be sometimes more

incomplete.

And as I said this morning, sometimes you walk into the room and you see the child and you know he's autistic, yet you have to spend time to do the --

Q Sure. And then among the patients that you have where you've diagnosed them as autistic, do you have a sense of how many of those children have gastrointestinal problems or symptoms?

A I can give you a range. It's important I answer the question about that because it has been on the agenda to now we ask questions about gastrointestinal symptoms, diarrhea, constipation.

I would think in my clinical load, it's about 10-15 percent, 20 percent at most that are reporting, many of them are functional symptoms which are not wearing pants and they disappear very quickly.

In our network we divide the medical clinic so we have a pediatrician who is there to investigate medical difficulties in the children. We can then refer to them if there is concern about diarrhea, constipation, diet, sleep or whatever. I refer to her, but very infrequently.

Q If you have any idea of what sort of treatments they use for those children that you refer?

A One thing that they do, they investigate the

diet of these children because it's very important to recognize that many of them have poor diet due to their behavioral restrictions, so they eat nonfiber food and other things which can lead to constipation and then overflow diarrhea. So dieting advice is an important aspect of the management.

Also some of them do have pica. They eat nonedible food, and that can create some GI problems. But again, it's not a huge proportion of the children I see, and these are children between age 18 months to five and six.

Q Do you recommend any particular diets for the autistic children you have? We heard a little bit of testimony here or references to things like the gluten-free, casein-free diet. Is that something that you recommend in your care and treatment of autistic children?

A No. We do not recommend, there is no evidence base study which would suggest that it's useful. There are ongoing studies to look at RCTs which are examining this question in Rochester, New York in particular. But so far it's not something that we advise to do routinely.

Q Do you do testing for urinary porphyrins for autistic children in your clinic?

A No. Usually not. Not in the standard child. Sometimes we have children where there are unusual dysmorphic signs so we refer them to medical genetic consultation, and then they do the full array of metabolic testing including this one.

MR. MATANOSKI: Mr. Powers, I think you're getting close to the end, but is there going to be a question about his Direct testimony coming up?

MR. POWERS: Yes, there are all questions that relate to what he does in his diagnosis.

MR. MATANOSKI: And how are they related to his Direct testimony?

MR. POWERS: Rather than asking me what I'm doing, I mean --

SPECIAL MASTER HASTINGS: He's making the point that most of these questions don't seem to be related to the epidemiologic --

MR. POWERS: But they're related to some of the causation factors. He talked in his presentation about, and certainly in the papers that were submitted today, the things I was just talking about. Gut symptoms, bowel symptoms, symptomology, when they appear, how far away the appear from a vaccination. I was just trying to spend a few minutes to explore those issues simply to see if there's anything he can

say about what he does in his diagnostic program that would inform the causation opinions he was talking about.

SPECIAL MASTER HASTINGS: I remember him talking about epidemiologic stuff this morning, but I'm going to give you some leeway on --

MR. POWERS: There truly is like a couple of minutes.

SPECIAL MASTER HASTINGS: All right. Go for it.

MR. POWERS: And it --

SPECIAL MASTER HASTINGS: Go ahead.

MR. POWERS: That might have been it.

(Laughter.)

MR. POWERS: That was it actually on diagnoses and clinical management. Then just a question, and I don't know if you know this.

BY MR. POWERS:

Q As you understand, I'm sure there will be additional test cases that are going to be heard here. Do you plan on coming back to testify and offer Direct testimony in cases, particularly on cases with the theory that Thimerosal-containing vaccines independent of the MMR are implicated in autism spectrum disorders?

MR. MATANOSKI: Actually, that's a question that goes to our approach here in terms of the attorneys. I don't think he's qualified to answer it. Whether I decide or the Department of Justice or Health and Human Services decides, what they decide to do in the upcoming cases is a matter of our trial strategy.

MR. POWERS: But he, and you're not his attorney, and I'm asking this witness whether he is planning --

MR. MATANOSKI: Whether he appears or not is going to be a decision made by the Department of Justice and Health and Human Services, not by the witness.

THE WITNESS: I am planning to go back to Montreal tonight because I have a clinic tomorrow morning, and that's what I want.

BY MR. POWERS:

Q So you don't want to sit around in the room and listen to additional testimony from other witnesses any more?

A No, it's enough.

Q And about how many hours of time did you spend sitting in the room listening to witnesses in this case?

A I don't know. You've seen me.

Q A ballpark?

A Maybe five days.

Q And during the time that you were listening to other witnesses when you were not testifying, were you getting paid for the time that you were here?

A I don't know yet.

(Laughter.)

Q There are a lot of people who don't know if they're being paid for their time.

A I hope I will.

Q I think that would be the expectation from your end, I'm not surprised.

Have you submitted any sort of bills or invoices to the Department of Justice for your work in this case so far?

A Yes, I think one or two.

Q Do you have an idea of how much money you have billed so far to the Department of Justice in this case?

A No. I've received nothing.

Q In terms of that you've billed with an expectation. Do you have even a ballpark number?

A No, because I don't have it in front of me so I don't know.

Q How about payment in other cases in which you've testified? I know the Jordan Easter case in Texas, you gave a report, you did a deposition, you testified at a Daubert hearing. Do you know what you ultimately billed the Defendants in that case?

A I spent like three days in Marshall, Texas.

Q Which is a beautiful place to spend three days. I was actually there the day that you testified --

A Oh, really. So yes, I recall that stay in Texas. No, I don't recall, I don't have any precise figure. I think last week I mentioned that $60,000 or $70,000 was probably an accurate estimate.

Q And then in other civil cases where you've testified, do you have a cumulative number? I really don't want to spend a huge amount of time on the issue, but really what I'd like to know is, for the entire time that you've been involved in litigation related to Thimerosal or MMR being associated with autism, anything related to those cases, do you have an idea of how much money you've been paid or expect to be paid? An aggregate number?

A No, I really put everything in a shoe box and go to the tax man at the end of the day, so I don't know. I don't know. I probably spend on

average 10 to 15 hours a month, on average.

Q And in the civil cases billing what? $500 an hour?

A Yes.

Q And in the DOJ, in the cases in this program, $250 an hour?

A That's my understanding.

MR. POWERS: I have nothing else for this witness. Thank you.

MR. MATANOSKI: All right. Tom, you were going to clear up one matter from --

MR. POWERS: When we're completely done. I don't know if you have Redirect.

SPECIAL MASTER HASTINGS: Any Redirect for this witness?

MS. RICCIARDELLA: We do. Can we take a five minute recess?

SPECIAL MASTER HASTINGS: Okay. Let's take our afternoon break at this time. Let's take a 10-minute break.

MS. RICCIARDELLA: Thank you.

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: We're back from our afternoon break. Dr. Fombonne is still on the witness stand and now we'll have some Redirect

Examination by Ms. Ricciardella for the Respondent.

MS. RICCIARDELLA: Thank you, Special Master.

REDIRECT EXAMINATION

BY MS. RICCIARDELLA:

Q Just a few questions, Mr. Fombonne. I have to speak up because I'm getting the same "battery low" message that Mr. Powers got.

You were asked at the very start of your Cross-Examination about different phenotypes, what different characteristics can classify as a phenotype of autism. But you and others have studied the particular phenotype that is at issue in this litigation, namely autistic enterocolitis, is that correct?

A Yes.

Q What have those studies shown about this particular so-called phenotype of autistic enterocolitis?

A The studies by and large show there is no validity to this particular phenotype as a separate entity. So the notion that it would be regression occurring days after the vaccination in a child with previously absolutely normal and will regress with GI symptoms is not supported by most data which has

looked at this question so there is no evidence of increased rates of regressive autism after MMR is introduced or it doesn't decrease when it's removed, the ascertation with GI symptoms is ambiguous. There is no evidence that GI symptoms have increased in autism over time. And there is certainly no evidence that the regression occurs more than in non-regressive cases just after the vaccination. So that's very clear from the range of studies which have replicated these findings.

Q Now there was also discussion, Mr. Powers asked you about congenital rubella and Thalidomide. Now those exposures, of the children who had exposure to congenital rubella and Thalidomide who later developed autism, are those exposures prenatal or postnatal?

A No, these are prenatal exposures. They are part of a small set of environmental prenatal exposure which has been documented to increase the risk of autism. So a few medications like misoprostol and others, lipoic acid, Thalidomide, maybe terbutalene and other kinds of events occurring during pregnancy are known to increase the risk of autism in some fetuses. But there is not much evidence of postnatal environmental influences. There

are a few maybe case reports which raise the possibility, but what we know about environmental factors so far is entirely confined to the pregnancy or the post-conception weeks. That's very clear.

Q You were also asked about different diagnostic criteria that make up the *DSM-IV* and the *ICD-10*. If I take a child, the same child, and I have one clinician applying the *DSM-IV* criteria and another clinical applying the *ICD-10*, are the two clinicians going to come up with the same diagnosis of the same child?

A Yes, absolutely.

Q And the studies that use either the *ICD-10* or the *DSM-IV* criteria, there's no mixing and matching of criteria within a study, correct? The investigators use a consistent criterion, either the *DSM-IV* or the *ICD-10*, in each study.

A I think what matters, within a study people would tend to stick to one particular set of diagnostic criteria, and within that framework you can therefore assess association with exposure or trends over time, provided that you don't shift diagnostic systems as you go along.

But having said that, *ICD-10* definition of autistic disorder is closely comparable to *DSM-IV* and

there is no differences of views or algorithms when we use *ICD-10* in European countries or *DSM-IV* in North American countries. It's pretty much the same. There are a few differences regarding PDD-NOS, but they can be made up to be comparable.

Q Doctor, Mr. Powers showed you a 27 page review article by Craig Newschaffer which you hadn't read, and of the 27 pages he asked you to comment on one sentence, actually half of a sentence found on page 239. What he didn't ask you to comment on was the second clause of that sentence that states, "...because it is very difficult to develop quantifiable estimates of diagnostic effects and virtually impossible to prove or disprove temporal changes in autism population risk profiles given the condition's unknown etiology."

Do you have any comment on that phrase and the entire paragraph that Mr. Powers asked you to comment on?

A I disagree with that second part of this paragraph. It says because the disorder is of unknown etiology you cannot assess temporal change in the rate of this condition which is absolutely, it's an ill-informed statement in medicine. People have looked at trends over time, recorded the incidence of disorder

of various disorders without knowing the etiology. It's actually a mean to progress in the understanding of the etiology of a disorder to collect epidemiological data, time trends, to compare rates across nations, across areas. It can be done provided that you have a reliable definition of what you study, even if you don't know the etiology.

So I really disagree with this part of the statement which I think is not well informed.

Q Doctor, you were also asked about slide 7 of your presentation today. It was a Finland study. That study done out of Finland, that study wasn't designed to test what the prevalence rates of autistic spectrum disorders were at that point in time, correct?

A No. The point of that slide is not to look at prevalence or whether or not it's accurate or not. Whatever is the prevalence in that city doesn't matter to the demonstration which showed that on the same children, same study, if you apply different criteria the old criteria give low rates; the more recent criteria give three-fold higher. That is what is the take-home message of that study.

Q Doctor, you were asked a question about your 2006 Montreal study. There was some confusion about

the term population, if it truly meant population as lay people mean it or a sample. You answered a question about uptake in prevalence and I think there might be some confusion.

In your Montreal study, why did you not use prevalence data for the same sample that you had chosen because of the vaccine uptake?

A We often prevalence data from a sample which is representative of a given population in a given area. Then the next question was to opine some kind of estimate about trends in vaccine uptakes to compare it to the trends in the prevalence that we had.

As we had data about vaccine uptake rates in the same geographical area from where we did our study, that would have been the best approach, but we didn't have such data. The next thing that we could go for would be to look at a few isolated studies in Montreal which were done with different samples, different methods over that study, so they would even not be comparable from survey to survey. So assessing the trends in that condition would be very difficult.

In addition, the whole island of Montreal is very disparate in terms of there are some regions, some areas big, and so there are wealthy areas, impoverished areas, and depending on where you do your

survey to evaluate vaccine uptake would affect your results.

So to compare to a particular privileged area, Montreal was not offering data that you could use. The only data we could really use was the Quebec City regular surveys in a sort of an area where the population is wealthy, there is not much of unemployment rate, and the survey were conducted most years with the same methods, and that allowed us to estimate the vaccine uptake for MMR over time and get this trend that we want to obtain. The rise of additional population is less than optimal, but it's the best that we could do. That would be done in most ecological studies.

Q To stay on the topic of ecological studies, Mr. Powers was discussing ecological studies and suggesting that your reasoning wasn't taking into account changes in case ascertainment, changes in diagnostic criteria, et cetera. Now in ecological studies, though, do trends on prevalence rates of autism change when you add MMR vaccines or Thimerosal-containing vaccines into the, when they're introduced or discontinued in the population?

A No. The idea is that if we, changing diagnostic criteria or certain ascertainment can

affect the results when you want to estimate the magnitude of a condition in a given population. so that would affect the point prevalence rate at a given point in time. Now when people generate trends, what you want to have is the trends are evaluated with methods which are more or less constant, so there is no major change in diagnostic content, or a major change in diagnostic criteria, or there is no suddenly a new ascertainment which is made in a population.

So provided that you have your methods of counting the cases which are uniform over time, then you can assess a trend.

Your methods could be not optimal. You could, for instance, in assessing trends in the rates of autism, only identify 70 percent of the cases in a population. And if you identify 70 percent of the cases in the population constantly over time then your trend will be actually an accurate trend even though the level of the rate is not accurate. The trend will be accurate.

So under such circumstances if you have a trend which is well estimated, then you can really look at the effect of vaccination policies and traditional new vaccines, removing that vaccination, and see if it affects the trend. That's what you do.

It has been done in various studies I quoted this morning.

Q One more question.

Doctor, there was some discussion towards the end of your Cross about different ways that you diagnose a child with autism. Although to assess early signs and symptoms of autism, can you use home videos as a tool to look at what are potential early signs and symptoms of the autism in that child?

A Yes, we do that in our clinics these days. we have often parents who come with videos or DVDs because they have observed unusual behaviors in their children that we are unlikely to observe in our clinics. When there are some unusual repetitive movements, for instance, we sometimes don't see in our clinic during the time of the assessment. It's a new place, the child doesn't really behave in the way he behaves across time, across context, the way the parents see him. So videos in that respect are often used by parents to document a behavior which they see that we will not see. So they provide this as evidence that we use. We use, we incorporate that evidence in our diagnostic assessment.

The home videos have been particularly useful to look at early signs of autism, predictors of

later autism diagnosis. The studies we reviewed last week have been extremely influential in trying to pinpoint particular communication and social abnormalities which can be seen at age 10 and 12 months in young babies which have subsequently been diagnosed with autism, even though parents do not recognize at the time of the abnormalities that they are abnormal behaviors. But the studies are really unambiguous in their findings by using these videos, looking at early signs of autism. You can predict a little autism diagnosis with a high level of accuracy.

Q One final question.

You were asked a series of questions about the Verstraeten study, using the Vaccine Safety Datalink. Doctor, did you look at Petitioner's Exhibit 91 from the Autism Omnibus proceeding which is the reanalysis done by the PSE's own experts, Doctors Uatin and Lalley?

A Yes.

Q Do they not state, and I quote, "We generally believe that the methodology employed by the CDC investigators was sound and that their findings are valid. Do you recall that statement?

A Yes, I read the reanalysis and this is their conclusion.

MS. RICCIARDELLA: I have no further questions.

SPECIAL MASTER HASTINGS: From Petitioners, any further questions of this witness?

MR. POWERS: Just a couple. Literally a couple. The questions are quick, I anticipate the answers will be quick, too.

BY MR. POWERS:

Q Dr. Fombonne, you mentioned when I was asking you questions earlier that your rate of gastrointestinal symptoms was about 10 to 20 percent in your autistic children. Do you remember that?

A No, you asked me to guesstimate in my clinic. You should know that in my clinic hospital children are referred to our program as opposed to going to neurology, for instance, because they have different degrees of mental retardation. So it's based on my particular program which has a high number of children, so that's what it is.

Q Then in 2006 you were the co-author on a paper with D'Souza and Dr. Ward who testified earlier. Do you recall that paper?

And in that paper on page 1669, gastrointestinal symptoms were reported in almost 80 percent of children from the autistic group. Do you

recall that?

A Yes. I think we probably have chosen the children for this particular reason because we were looking again at the autistic enterocolitis phenotype.

Q Okay. The number jumped out at me and I just wanted to --

A Yes, but just to elaborate just one minute on that.

Q Okay. And I'm listening, but I dropped something, so I'm picking it up.

A All right. The way gastrointestinal symptoms is assessed in various studies is highly variable. People sometimes ask the question, has your child ever had diarrhea and constipation? If you ask this question in this room the rate will be 100 percent, you know? Then people sometimes do three months in a row. So the way the question is asked can really influence the actual rate.

If you look at studies where GI symptoms rate have been published, there is a complete lack of standardization in how you define, how you measure GI symptoms. But pediatricians report, by medical records, by parental reports, how far did you go back? Did you impose a duration criterion for the symptoms to be counted? It's very, still complicated, but it's

very haphazard across studies. Hence we have rates which vary enormously.

Q You mentioned also earlier that you had a six year old patient with pubic hair. Was that a precocious puberty case?

A Yes.

Q Do you see that often in your practice? Precocious puberty?

A No. It was one case.

Q Again, just curious.

Finally, in the materials you talked about the autism epidemic. Have you heard any allegation in Petitioner's case in chief that relies on the existence of an autism epidemic of proof of causation in the Cedillo case?

A In the Petitioner's documentation? Many studies have been referenced, we make that claim.

Q I'm just talking about the case that was put on, have you heard any allegation that the finding of an epidemic of autism is part of the proof that Petitioners are relying on here in the Cedillo case?

MR. MATANOSKI: Actually, Tom, there was Cross on that that presented that as a postulate. Not of this witness.

THE WITNESS: My understanding is that

Wakefield hypothesis is significant in that particular case, and it was one of his claims. So his theory is tied up to this idea.

BY MR. POWERS:

Q So it was from Wakefield that you see it, correct?

A I think so, yes.

MR. POWERS: Nothing else. Thanks.

SPECIAL MASTER HASTINGS: Anything further for this witness?

MR. MATANOSKI: No sir.

(Witness excused.)

SPECIAL MASTER HASTINGS: Should we start with the testimony of Dr. Griffin?

MR. MATANOSKI: Yes, sir.

SPECIAL MASTER HASTINGS: Dr. Griffin, please take the witness stand.

MR. POWERS: One thing, just for the record. In my Cross-Examination of Dr. Wiznitzer we discussed the possibility that he might have testified as an expert witness for the defense in the case of Jordan Easter. I found that was simply a miscommunication with the Plaintiff's counsel. Dr. Wiznitzer did not testify or appear as an expert witness in Easter and I didn't want to leave the impression that he had and

was being disingenuous. As a matter of fact, he has not.

SPECIAL MASTER HASTINGS: Thank you for clearing that up, sir.

All right. We have Dr. Griffin at the witness table, and Dr. Griffin, I'm going to ask you if you'd raise your right hand for me.

Whereupon,

DIANE GRIFFIN

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

SPECIAL MASTER HASTINGS: Please go ahead then, Mr. Matanoski.

MR. MATANOSKI: Thank you, Your Honor. I'm hoping that we keep this brief. We don't have a whole lot of slides, and I'm not real familiar with using them. I'm going to try to tell you which slide we're on.

SPECIAL MASTER HASTINGS: All right.

MR. MATANOSKI: I may forget. I may be like the person at the light and the light goes green and you're waiting for them to pick up on it. If you give me a moment, I may pick up on it. If not, give me a little toot on the horn to let me know that I've forgotten to say which slide we're on.

SPECIAL MASTER HASTINGS: All right. Do we have a handout you're going to give us?

MR. MATANOSKI: Actually Mr. Rooney will be giving out a handout right now.

MR. ROONEY: May I approach the bench?

SPECIAL MASTER HASTINGS: Yes, please.

(Pause.)

SPECIAL MASTER HASTINGS: All right. Let's mark this as Respondent's, I think we're up to 22, so this will be 23.

DIRECT EXAMINATION

BY MR. MATANOSKI:

Q Good afternoon, Dr. Griffin.

A Good afternoon.

Q Could you start with telling us a little bit about your schooling? We could start with where you want to college.

A I went to college at Augustana College in Rock Island, Illinois, where I got a BA degree in Biology.

Q From there where did you go?

A From there I went to Stanford University Medical School where I got an MD and a PhD. the PhD was in immunology where I was studying immunoglobulins.

Q After that, what path did your career take?

A My path went to Johns Hopkins where I've been ever since, so I have an easy CV. I did a post-doctoral fellowship with Richard Johnson who is a neurovirologist and we went to Hopkins because my husband was a neurology resident. And after a post-doctoral fellowship with Dr. Johnson, then I joined the faculty in the Department of Medicine and Neurology. I've always had a joint appointment in those two departments. Where I progressed through the ranks to Professor. Then in 1994 I became Chair of the Department of Molecular Microbiology and Immunology in the Johns Hopkins Bloomberg School of Public Health. So I moved across the street, but I retained my appointments in the School of Medicine.

Q Doctor, first of all could you try to speak a little slower?

A Okay.

Q Right now, this late in the day, my mind is working very slowly. If you could try to speak a little slower, that would be great.

How long have you been at Hopkins?

A I went to Hopkins in 1970 so I have been there ever since. That is 37 years. If my math is correct.

Q As Chair of the Department of Molecular Biology, I hope I got that right.

A Molecular Microbiology and Immunology, but you're not the only one who gets confused.

Q What do your duties entail?

A I'm Chair of the department so I have a lot of administrative duties with respect to both university affairs, school affairs, departmental affairs, faculty mentoring, faculty recruitment, faculty promotion, all the things that go with running a department, basically, and then in addition, it's sort of a typical academic appointment, I also have my own research program so I have a research program that's in viral pathogenesis, and we'll talk I guess more about that later. But in addition to that, so I spend a substantial amount of time mentoring people within the lab, going over data, writing papers, et cetera, that are related to the research component.

Then there's the third component of education that is a more formal education kind of process, teaching the graduate level virology course, lecturing in a number of other courses, teaching medical students microbiology, that sort of thing.

Q I don't want to belabor what's on your CV, but if you could just go through some of the

professional societies that you belong to that may have application to what you're going to testify here today.

A I belong to societies that are relevant to infectious diseases. I'm a fellow of IDSA, the Infectious Disease Society of America. I'm in American Society for Virology, in fact I was President of that organization. I'm a member of the American Association of Immunologists. I am, the other things that are relevant. Well, I'm a fellow of the American Academy of Microbiology. I'm a fellow of the American Association for Advancement of Sciences. Then I'm also a member of the Institute of Medicine and also the National Academy of Sciences.

Q With respect to the Association for the Advancement of Sciences, did you hold a special position there?

A I was, in fact I'm retiring Chair, past Chair, something like that of the Medical Sciences Division of the AAA, yes.

Q With respect to journals that may have some application to what you're going to testify to here today, are you on the editorial board or an editor of journals in say virology or immunology?

A I was an editor for 10 years of the *Journal*

of Virology. I'm on the editorial boards of the *Journal of Clinical Investigation of Virology*, of the *Journal of Neurovirology*. I'm an editor of the *Proceedings of the National Academy of Sciences*. Those are probably the main editorial things I'm doing now.

Q When did you begin studying the measles virus?

A I started as a post-doc, probably in 1973 or 1974 we first started getting interested in measles. So as I mentioned, I went to Johns Hopkins as a post-doctoral fellow in sort of neurobiology and infectious diseases. I combined clinical training at the same time with research training during that period of time.

I was studying primarily encephalitis, alpha virus encephalitis. As I mentioned, the laboratory was particularly, it was a neurovirology laboratory. I was interested in virus infections of the nervous system.

One of the diseases that has been very puzzling and actually still is very puzzling, is a post-infectious encephalomyelitis that can complicate a number of viral infections, but it particularly complicates measles.

Dr. Johnson had done a sabbatical, a period of time in Peru where they were seeing actually quite a large number of cases, they had endemic measles at that time, were seeing quite a large number of those cases so we thought that would be an opportunity to try and understand better how that particular complication occurred.

Subsequently we understand it as an autoimmune disease that occurs in close association with measles. It's not a progressive disease. It's a rather characteristic disease that occurs primarily in people who get measles when they're older, usually five or ten. In that particular population in Peru there was a lot of in migration, so there were a lot of older people getting measles, sort of an unusual situation.

Q What prompted you to study the measles virus in particular?

A As I say, we started because we were interested in this neurologic complication and we thought that, as a part of that we were studying those patients that had that particular complication and then comparing them to patients who didn't have that complication. So those were children that either had measles with no complications or had measles with

other infectious diseases which is the most common complication of measles. So we'd stratify the patients into these three groups basically. Then also patients usually that had other, similar age children that had other infectious diseases as a control group or no disease.

Q I can tell from your resume, you continued with studying measles virus. Why did you --

A Right. What our initial studies found was that, our original hypothesis was their was going to be something different about the immune response to measles that was occurring in these children that got the neurologic complications versus the ones that didn't, that got other complications.

What we found is that they all had this immune suppression that was very profound and that occurred in association with the acute disease, and it really wasn't different between the different complications of measles. It wasn't identifiably different in a way that helped you to try to figure out what the difference was between them. So consequently we got interested in what's measles immunosuppression, what's that biologically, and how can you understand that particular problem. Then subsequently we got interested in other aspects. It's

a fascinating disease biologically, and it's an interesting virus. It just progressed.

Currently we're doing a lot of vaccine studies to develop a vaccine that could be used in younger children. Protective immunity. What does a vaccine have to do in order to protect you from getting infected? We continue to study immunosuppression in measles. We could study clearance, what aspect of the immune response is important for clearing the virus? Those are all questions that are ongoing at the moment.

Q So you've not only studied measles virus but you've also studied the effects of immunization with measles vaccine?

A Absolutely, yes.

Q Do you know offhand about how many published articles you have on measles virus or measles virus vaccine or MMR?

A I don't know for sure, but I would guess around 100, both peer reviewed primary publications and review articles and chapters and that sort of thing. I would imagine it's in that park.

Q I know this is covered a bit in your CV, but the book, "Fields Virology", what is that book?

A Well, it's sort of what most of us consider

the bible for virologists. It's a big, fat, two-volume book that you go to that's in its fifth edition, that you go to when you want to look up anything you want to know about those particular viruses. It's too fat for a textbook. It's a reference book. It really is a reference book for virologists.

Q Did you contribute to that book?

A I'm an editor on that book and also I've written two of the chapters, one on alpha viruses and the other on measles virus.

Q How long have you been contributing a chapter on measles virus to --

A I think I've done the measles chapter the last three editions, so the third, fourth and fifth edition. They come out about every four years or so.

Q Do you write any other book chapters with respect to measles virus?

A I write and review book chapters regularly. Well, I'm trying to avoid it because they're really time consuming. For a number of different other books, compendia of articles, et cetera. I'm editing one right now, actually, for current topics in microbiology and immunology on measles. Michael Oldstone and I are editing that.

Q I'm sorry, with whom?

A Michael Oldstone. He's a virologist in -- He also works on measles at the Script institute, so the two of us are putting together, we're editing currently a book on measles. It's sort of an anniversary of the vaccine.

Q I'm going to ask you some questions about whether you've been in the courtroom before and any contacts you may have had with litigation before.

You're doing fine so far on the witness chair. This isn't why I'm asking you that.

Have you ever testified before?

A I've only testified once before, which was in a malpractice case before, it was a board in Maryland that hears, it's not actually a courtroom trial, it's maybe sort of like this. There's a person or two or three that hears a case before it, adjudicates, basically, malpractice cases. I disliked the experience greatly, and have avoided it ever since until now.

(Laughter.)

Q How long ago was that?

A That probably was 20 years ago.

Q And it will probably be 20 years before you --

A Well --

(Laughter.)

Q Did you ever work though, besides testifying, did you ever work on litigation involving MMR vaccine?

A As I say, I have studiously avoided any request to get involved in any kind of legal issue ever since my first experience, really until this came along, and I just thought it was such an important issue to make sure that we get it right, that I agreed. So this is one of three things I've been involved with with respect to MMR.

Q The other two, one of them was in the United Kingdom?

A Right. So I was involved in the U.K. litigation or failure of litigation. Putting together the information at least for the judge in that case.

Q The information on measles virus --

A On measles vaccine, right.

Q The other piece of litigation that --

A The other, and that is still pending. There's at least one case pending against Merck that I've consulted with them on and written an expert testimony on that's here in the U.S.. I think independent of this. I don't know exactly how they

fit together. But that hasn't gone to trial yet. I don't know what the status is.

Q I'd like to talk now a bit about measles virus, and right now, until I change we're going to be talking about wild measles virus.

Can you tell me how wild measles virus is spread? And we're going to put up a slide here, I think.

A The spread in a population is a respiratory spread. So basically people shed the virus in their respiratory tracts and that's how people, it's a very infectious virus. It's one of the most infectious agents that we have, the wild-type virus.

Q This slide we put up is Slide 1. So far Dr. Griffin has not talked about that yet.

A No.

Q Feel free, I just was giving you the opening to talk a little bit about wild measles virus. It spreads by --

A It spreads through the respiratory tract, so basically by respiratory droplets and being exposed to someone. So it's similar to the way influenza would spread or actually chicken pox spreads the same way.

So you breathe in the virus and, as I say, the wild-type virus is very infectious which is

interesting. It's very difficult to grow it in tissue culture, but it knows how to infect people. We don't completely understand how it's so efficient at getting from one person to another, but it definitely is.

Q After it enters a human, what happens next? And if you'd like to refer to the slide at this point, feel free, if it helps.

A This is actually from my chapter in "Fields Virology" on measles to try to give the idea of the pathogenesis.

Basically it affects the respiratory epithelium, so it's the initial cells that it comes in contact with in the respiratory tract. Then from there it goes to, it's carried to the local lymph nodes. So the lymphatic tissue that drains the lungs. A lot of this we know from studying children, but we also know this from studying monkeys. This is a virus that's very restricted to humans, but it does also affect non-human primates and causes measles. All other animal models actually are not, I don't think they're useful for studying measles. Monkeys are and people are obviously.

From the local lymph nodes, and this is a very lymphotrophic kind of virus, it then spreads from the blood. So cells that get infected in the lymph

nodes and can leave the lymph node, that's what we call a cell associated viremia in the blood. So it's in lymphocytes and monocytes are the main cells that are infected that are circulating in the blood, and undoubtedly the main cells that are infected in the lymph node as well and other lymphoid tissue.

Once it gets into the blood it spreads everywhere. We know it spreads to the skin because you get a rash. But there are often liver abnormalities, there can be cardiac abnormalities. It can certainly spread to the gut. As I say, you find it in lymphoid tissues everywhere, but also it affects endothelial cells and epithelial cells in addition to the lymphoid types of cells. So because it does that, you can find it in many organs.

Q Now, Doctor, on the bottom of Slide 1, you have a series of numbers. What do those numbers represent?

A Those are days after infection. As you'll see from a couple of subsequent slides, the line is sort of the amount of virus. It's a crude estimate of the amount of virus. So as it's spreading, you're increasing the amount of virus that's present in the body in general. Then you can see the line then goes down. That's around, the peak of the viremia and the

spread is around somewhere between 9 and 14 or 15 days typically.

Q Again, this is with the wild virus.

A This is with the wild virus. This is everything with the wild virus. Right.

Then it starts to get cleared. Then that's a manifestation of the immune response once it starts getting cleared.

Q You mentioned that it's specific to humans and some non-human primates. Then you said you didn't think other models of other viruses were that helpful or useful.

A That may be my bias.

(Laughter.)

Q What do you mean by that?

A What I mean by that is that there are, monkeys get a disease that is in every way similar. They get a rash, in every way it's similar, spread by the respiratory tract, et cetera, as humans get. But it's hard to study monkeys and it's also hard to study people. So most people if they want to study this interesting virus would like to study something smaller. A mouse would be nice. Unfortunately the receptors that measles virus uses are, and we'll talk about this later, user probably two or three different

receptors, aren't present in mice. Therefore the mice don't really get infected. You can sometimes put it in through the brains and get, which is not exactly a natural route of transmission for the virus.

People have made what they call transgenic mice which is to put the human receptor into the mouse to see if now they could get a measles-like disease, but still the replication is very restricted and again, doesn't mimic, you can't use a respiratory tract route, et cetera. It just doesn't mimic the disease.

Q Do you think that using, I may get the names screwed up here, but do you think that morbilliviruses compare to measles virus readily in terms of how similar they are, what results can be expected?

A Measles is within a subgroup of the paramyxo variety, which includes a number of interesting human pathogens like monks, for instance, like respiratory syncytial virus. But within the morbilliviruses, measles is the human version, the morbillivirus is. As I mentioned, they're very species specific, all of the morbilliviruses.

There are morbilliviruses that infect dogs, canine distemper; seals. The one that's most closely related to measles actually is rinderpest virus which

causes a disease in cows. So it's thought that the origin of measles was moving, was a transfer from cows in early herding societies into human. Whether that's the case or not, I don't know.

Those are interesting viruses. We certainly learn from studying them and they cause interesting diseases in their own particular hosts, just like measles does in the human host.

Q But measles are specific to humans?

A It is. And monkeys. Because monkeys can get it naturally from humans.

Q You mentioned that it hits the lymphatic tissue. Would that mean that it's lymphotrophic?

A Well, yes, that certainly is a primary site of replication is in lymphoid tissue, but it's certainly not the only site. As I say, it also replicates in epithelial cells and in endothelial cells. We think we know the receptor for the lymphoid, a lot of the lymphoid replication, which is a receptor known as SLAM for this wild-type virus, but we don't really know how it gets in and what the receptor is in epithelial cells of endothelial cells, but those are clear targets for the virus.

Q Does it preferentially select tissue in the gut?

A No, as I say lymphoid tissue anywhere and it will infect epithelial cells any place, both of which are represented in the gut.

Q So it just spreads throughout the body.

A Yes. In fact I don't even think gut made my slide here, but it could be included as could the heart which also isn't on there.

This is a systemic virus infection.

Q What about the brain then?

A The brain is interesting. We've done a number, again, in connection with studies that we did in Peru, we did autopsy studies of children who were dying with measles acutely specifically to look to see where the virus is. We found it in all these places, the usual suspects. But when we looked in the brain, we could find it only in endothelial cells. So we could find brain vessels. The lining of the vessels infected in a few people that we looked at. We didn't find it initially, they use a pretty sensitive technique, to be able to find that. But we never found it in actually the brain tissue itself. It was just in the vessels.

Q But it was found throughout the --

A Well, no, no. It was one here -- You could find A positive vessels, put it that way.

Q In these patients where you found it -- let me step back. You found it in the blood vessels in their brain?

A Right.

Q You didn't find it elsewhere in their brain?

A No place else in the brain. And that was also true of the patients, as I mentioned that we were studying that had this post-infectious encephalomyelitis. Actually we couldn't find it any place in those individuals, but presumably they did have this vascular or endothelial lining infection earlier and it was just gone.

Q But could you find it in the same patients in other tissue in their body?

A Oh, sure. Yes, it was much easier to find elsewhere. We had a harder time finding it in the brain.

Q Was it widespread?

A Oh, yes. The spleen, the lungs, the skin. Most places, the gut. Most places we looked you could find it, particularly if you looked in lymphoid tissue that was associated with that particular organ. But we found it in the liver. It was very widespread.

Q When you looked in the brain did you see it in the neurons?

A No. As I say, it was only in these vascular endothelial cells. It looked like it was unable to spread out of that spot.

Q And I take it then not the astrocytes or the microglial --

A Not in, we're talking about acute wild-type measles. We have a different story with SSPE and other neurologic complications, but for acute measles you don't find it.

Q I want to turn now to the clinical symptoms of wild measles virus infection. If you could talk about those please, and what's going up now in front of the Court is Slide 2, and feel free to refer to that at any point during your discussion of the clinical symptoms of elucidates the discussion.

A We'll put all this together at the end, but the clinical symptoms, the way that measles is recognized is usually with a rash. And so clinical measles gets diagnosed. An astute physician in an outbreak situation may be able to see Koplik's spots which are little spots on the inside of your mouth in children who come in with a fever.

As you can see, the black line is the fever. As I mentioned earlier, the peak of the viremia is occurring around between days 10 and 15. During that

period of time is also when you start to see the earliest symptoms.

So one point is the first ten days of infection are relatively asymptomatic. There's a lot of virus replication going on of symptoms until usually the prodromal period which is maybe for two or three days before the onset of the rash when there is fever, there can be conjunctivitis, cough, some, we call them prodromal symptoms before the rash appears. Then the rash appears and it's three or five days of rash is typical.

Q If I take it from this slide, when the rash is appearing is that really towards the end part as the infection has started to clear?

A Yes. In fact it correlates with -- The onset of the rash correlates with the initiation of appearance of the adaptive immune response and the initiation of virus clearance is occurring during the rash phase.

By the time the rash is over, the fever is over, usually the child feels, assuming no other complications, feels perfectly fine. Home.

Q And the line on the bottom, the numbers on the bottom again are --

A Days after infection

Q Do you see diarrhea as one of the clinical symptoms of measles infection?

A Diarrhea is not uncommon, and it really depends a lot on what population you're studying. As I say, the populations that we've studied in most depth are in developing countries, either in Peru or in Africa. But we certainly have done some studies within the U.S.. But in Peru where we did the most in-depth studies, diarrhea was very common but it was almost always due to another infectious agent. It might be salmonella, it might be shigella, it might be entamoeba histolytica. There were lots of things that caused diarrhea in those --

Q That last one's going to give the court reporter a fit. We'll spell it afterwards.

A But all I'm saying is that in those populations diarrhea is a common -- there are a lot of things that cause diarrhea in that population. Basically what the children with measles got that got diarrhea, they generally reflected what was going on in the general population. So if there was a salmonella outbreak, then they were more likely to have that, et cetera.

But usually the diarrhea could almost always be ascribed to another diarrhea-causing agent that was

there at the same time.

Q If I take that right, then the diarrhea wasn't necessarily caused by the measles, but rather - -

A No. Diarrhea isn't a very common symptom of measles per se. And certainly if you look at populations in more developed countries that have less problem with diarrhea causing agents, then, I won't say diarrhea is never seen, but it's not considered a common aspect of measles.

Q I want to turn to the immune system because we touched on it a little bit already. It's important obviously to this case.

If you could take us through sort of the timeline of what's happened with the immune system after the introduction or after the virus infection with wild measles virus. And sort of explain, we've gone to Slide 3 here, and it's the same format as the other two. If you could just take us through and tell us about the different parts of the immune system that are coming into play here.

A Right. The initiation of the immune response, what's here is pretty much what you can measure in the blood of an individual with measles. But the initiation of the immune response is really

starting at the time of the initial infection of the lymph nodes after the respiratory infection. So it's happening back at day one on this graph, although there is nothing in here that shows that.

There are cells that are resident in lots of places, but certainly in mucosal tissue like the respirator tract, dendritic cells that pick up pathogens. I mean their job is to take up pathogens that have been introduced wherever. It could be the gut, it could be the skin, it could be the respiratory tract. And carry those to the lymph node where actually you initiate the immune response. So these are what we call antigen presenting cells. These are cells that know how to process and present antigen and start stimulating T cell responses within the lymphoid teacher.

So probably what's going on in the lymph nodes during those first few days is quite complicated because we know the virus is replicating, but we also know that the immune response that's being initiated, cells the virus are replicating in are going out into the blood. But eventually you build up enough of an immune response. So you're stimulating, on this diagram we're talking most about T cells, CD4 and CD8 T cells which are getting stimulated by the measles

antigen. So within the whole immune repertoire we have a small number of cells that will actually know how to recognize measles virus. So what you want to do in an immune response is to greatly expand those few cells that may be present and are measles virus specific as part of the normal repertoire.

So what's happening in those first seven or eight days is this really amplification of those cells that are specific. It's happening both for CD4 T cells, it's happening for CD8 T cells, and it's also happening for B lymphocytes that would be specific for the measles virus antigen. All of this is gearing up to have an adaptive immune response that is going to allow clearance of the virus.

Q Just for the record, Respondent's Exhibit D, I believe is Dr. Griffin's report.

Just to make sure I have a good understanding of what's happening with the T cells, in your report you were talking about naive cells and differentiation. Is that what you're talking about here?

A Exactly. They start out, the cells start out naive in that they have never seen measles before. And so now what you want to do is select those cells that know how to respond to measles and that's done

through this antigen presenting cell process which is very complicated in stimulating the cells to proliferate, producing cytokines that allow them to proliferate. There's a lot of things going on to allow that expansion to occur, and for that expansion to be of the cells that are specific for measles virus. The ones that are going to be relevant to actually recovering from this infection.

Q So essentially the body starts saying we need to gear up this particular kind of cells to go after --

A Absolutely. Measles is a major challenge, the wild type measles is a major challenge to the immune system. In fact it was Burnett I think that says it was nature's way of figuring out who was immune deficient.

Consequently, it invokes a substantial immune response to the virus as part of that process.

Q What's the IgM and the IgG specify? What does that signify with the immune response?

A In addition to the T cell response which was crudely diagramed here as CD4s and CD8s, you also get an antibody response. And as I mentioned, T cells are amongst the cells that are being stimulated in the lymph node by the measles virus antigen resisting

cells. then the first kind of, and they also go through phases of development. The first phase is that they can make IgM. That's the first kind of antibody they can make, and they have to go through a differentiation process in order to make IgG which is what's going to be the long term response to measles, is measles IgG. That process of switching from IgM to IgG, particularly the very mature IgG response is a T cell dependent process. So these two things are intertwined. To get long-lived memory IgG you need T cells. In addition, T cells are doing their own thing with respect to virus clearance as well.

Q That's a concept I don't think we've heard before. In what way are the T cells helping the body switch over to IgG if you can explain in a form that's easy for us to understand.

A There's two processes of differentiation for B cells to be able to go from IgM secreting cells to what I would call mature plasma cells that are making antibody. For protection from reinfection, which measles is fantastic at. I mean you have lifelong immunity to measles once you've recovered from this infection.

Q Because of the IgG?

A Mainly because of the IgG. So to get that

long term secretion of IgG in the most mature form, two things have to happen to B cells. They're called class switch recombination and affinity maturation. Class switch recombination is moving from IgM to IgG and there are several types of IgG and you can also make IgA, but that actually involves a deletion. But that's a T cell dependent process to reorganize basically the DNA of those B cells so they now make IgG instead of IgM.

So the naive ones have IgM on their surface and they are of all different varieties. Now what you do is select the ones that are reacting with measles. They then get transferred to another place actually in the lymph node, the germinal center, where these maturation processes go on.

Affinity maturation takes a longer period of time and isn't totally independent but sort of independent of class switch recombination in that you select, progressively select the cells that make the best antibody. The ones that have the highest affinity for the antigen. That process actually occurs over months if you follow affinity maturation after this stage. That's also a T cell dependent process. That's what's necessary for the long term secretion of IgG after infection.

Q So basically you've got T cells working here, they're working in combination with your antibody response. Your IgM is kind of a first antibody response, but then after that it starts switching over to IgG. Is that pretty much what's going on?

A Right. And the IgM can be neutralizing. It's probably very important to help restrict virus spread in the body after you initiate the immunoresponse. So that's an important component. But it won't be long term. It might help you with the acute phase but it's not going to protect you from reinfection because it won't be around a long time.

Q You have a line here at the bottom that says immune suppression. What's that representing as far as the immune responses?

A That's one of the reasons we're sort of fascinated with measles. It's a very paradoxical kind of concept. At the same time all this is going on with measles, so you've got all these CD4 cells and CD8 T cells and antibody secreting cells, et cetera, being produced against measles. At the same time that the immune system is not responding normally to other challenges.

So most of the deaths due to measles are due

to other infectious diseases. Diarrhea was one example. For the most part that's not a fatal, diarrhea isn't a fatal complication, but pneumonia can be. All autopsy studies that look at what causes the death of children with measles show that what causes the death of children with measles are other infections, usually pneumonia. It's often bacterial pneumonia, it could be other viruses, but usually it's bacterial pneumonia.

So there is a period of time which is initiated during this acute phase that children are more susceptible to other infectious diseases. So this is a very clinically important complication or outcome or by product of measles and all of the data suggests that it's directly related, as I say paradoxically, to the fact that the immune system is so activated and so engaged in making an immune response to measles that it is not appropriately positioned to respond to some new challenge that comes along at this same time.

So in fact the immune system is working really well in this against measles, but it's --

A Right. As I say, that's one of the puzzles of this, why it's intriguing to us from a biological perspective to try to understand exactly what's going

on. It's complicated and we don't have all the answers, but those are the facts.

Q One of the concomitances that it leaves the body more susceptible to other --

A Other infectious diseases. But at the same time you're getting this -- I mean the immune response to measles is one of the best, as I say it gives you lifelong immunity. There have been studies that show on island populations that 60 years later if you recovered from measles, you're still immune to measles. So it's terrific.

Q We've been talking about each of these three different things, the replication and what's happening in the body, what's happening outside the body in terms of clinical responses, and what's happening with the immune system separately.

I know we've put these all together to sort of show one right on top of another so we can see what's happening overall. This is Slide 4.

A The main point of this in addition, just so you know what's going on with the virus replication, you know what's going on with clinical symptoms, and you know what's going on with the immune response is the fact that the rash is dependent on the immune response. It comes at the same time as the immune

response. Children who are immunosuppressed for whatever reason, HIV infection or whatever, can get measles without getting a rash. If they don't make a good immune response to measles, they won't get a rash, so it makes it hard to diagnose because that's usually the way we diagnose measles is with a rash. At the same time as the appearance of the rash which is coincident with the appearance of the immune response, you're getting clearance of the virus. So that period of time is the real manifestation of the measle specific immune response and virus clearance that are occurring during that period.

Q Is fever in any way related to the immune response?

A Oh, yes. That's when you see fever. You see fever during this rash period or just before, so that's my little line there that goes up just before the rash. Often there's fever for a day or two prior to the onset of the rash, but that is a manifestation of the immune response also. In fact, again, children who are immunosuppressed and so are not mounting this kind of an immune response to measles often do not get a rash, but they're often thought to have had very, if they're even recognized to have measles, it's said to have been very mild, that they weren't really very

sick. In contrast, I don't know how many people in this room have had measles, but most people who had natural measles remember it. It's one of those diseases that you remember because it's a very, you're really sick. You're in bed for a few days. It's just an unusual observation that if you don't get a very good immune response because of whatever congenital thing, you won't get as much fever, you may not even get a rash at all, so measles will appear to have been very mild.

Q With respect to, switch back to the immune system. You in your report had explained different phases to the immune response.

We've gone to Slide 5 now. This may help take us through the different phases.

A This isn't my diagram, this is a rather classic diagram of what happens during a viral immune response, but I think it's very relevant to discussing the immunologic aspects of this particular case because the immune system is not static. The immune system is changing all the time, and that's perfectly appropriate. This diagrams the kinds of things that are going on during a virus infection. This is just sort of a generic virus infection. So we talked a little bit about this in the measles context, but the

beginning is the entry of the virus, as you can see on the far left, and then these innate defenses. And there are a number of innate defenses that can come into play for virus infections. One of them, there can be production of cytokines. The most important cytokine for most viral infections that help to sort of restrict virus replication is a production of interferon. Interferon is very commonly produced during some of these early phases.

It may not be produced, we can't find it in measles. So a number of viruses that are particularly pathogenic, actually, have figured out how to block the interferon response in order to have a better chance of really causing a more severe disease. And wild-type measles appears to be amongst those viruses that can do that.

But you're marshaling macrophages. There are cytokines being produced that are important for the development of the T cells, et cetera, so the early phase of innate defenses and induction of the adaptive response are all sort of blended together.

Q Is this what you'd describe as the initial phase or the first phase?

A Right. This is the initial phase.

One of the important things during that

induction of the adaptive response and during the adaptive response is that you produce very large numbers of virus-specific lymphocytes, both CD4 and CD8 cells, undoubtedly in the lymphoid tissue we can measure it most easily in the blood, so a very large proportion of the T cells that are circulating may be directed against measles. We're all challenged with all sorts of different -- We need cells that do other things, not just measles.

So one of the things that happens during this late phase is, the memory phase, is that you have to shut off that immune response. Once the immune response has sort of done its job and cleared the virus, then you need to decrease the number of cells that are actually specific for that particular virus.

That dramatically decreases ten-fold at least. Then you're left with, this is the last phase, which is called the memory phase. There will be a much smaller population of cells than there was at the peak that are those memory cells that stay there, they continue to circulate. They're the antibody secreting cells that we talked about. That's one group. They go mostly to the bone marrow, but there are also T cells that are memory cells. If that individual gets the measles virus again, then those cells go back into

action basically

Q So far we've just been talking about the wild virus. I want to turn now to the vaccine virus, the attenuated virus. Basically we're going to talk about how it may be different from the wild measles virus. What does it mean when one says attenuated virus? What does that mean

A That means a virus that's lost its virulence. Usually it's been specifically attenuated, so virulent virus by definition here is a virus that can cause the disease measles. The attenuation process that was used in measles, it's probably similar. It was a very classic --

Q This is how they made --

A This is how they made the vaccine, to make the vaccine virus. As I mentioned, the virus is specific for, it's a very human primate tropic virus basically. The process of adaptation for this virus was to adapt it to grow in the non-human cell.

The idea was if it now learned how to grow in something else, in the measles case it's chicken cells, so they adapted it to grow in chicken embryo fibroblast. Once it now grew very well in chicken embryo fibroblast, it no longer grew so well in human cells.

So one of the things that it's done is actually changed the kinds of receptors that it can use and as I say, I don't think we still know what the receptor is on chicken cells, but there's a CD46 which was the first receptor that was recognized for measles, is actually recognized mainly by the vaccine virus and really not by the wild-type virus.

Q What was the wild-type virus receptor?

A SLAM. CD150 if you want a CD number.

Q And the vaccine is 46?

A CD46. That was the first receptor that was recognized, and that's not surprising because as I mentioned at the beginning the wild-type virus doesn't grow very well in the kinds of cells that we use in tissue culture. It's a pain to get enough of it.

So the viruses that grow very well and that everybody studies because they're easier, are these tissue culture adaptive strains or vaccine strains for the most part. So a lot of the literature on the in vitro studies of measles are really the vaccine strain of measles because you can work with it much more easily than you can with the wild-type virus.

Q You were mentioning that it's changed its properties now and I think you were saying it doesn't replicate as well?

A It doesn't replicate nearly as well when you inoculate it into a person or a monkey. So it replicates to a much lower degree. As I say, paradoxically, if you look at it in tissue culture it replicates better than the wild-type virus so there's clearly something we don't understand here. But if you look at it in a person or a money, the replication is almost, the viremia is almost undetectable for a vaccine strain of virus compared to the wild-type strain which causes this huge viremia.

Q I think you had a representation of that.

A I do.

Q This would be Slide 6.

A This was an experimental study that we did which was comparing lots of strains of measles virus. It was during a time that we were trying to identify a strain that we could use to infect monkeys that would give us disease, that would give us a rash and a viremia. So this is just the number of infected cells, basically, in the blood. The big peak, which is labeled wild-type is the kind of viremia you get when you inoculate the wild-type virus into a monkey.

There's another tissue culture adapted wild-type strain which is not completely attenuated, gives us the middle thing. Then there's a whole bunch of

vaccine and vaccine-derived strains which are all at the bottom. It was only every once in a while in one or two monkeys on one day or another that one might be able to detect measles virus. So the amount of replication of the virus is very much decreased compared to what happens with the wild-type virus. That was one of the things, many things were probably accomplished with attenuation, but this is probably the most critical in that it no longer really caused measles, but it replicated enough that it induced an immune response to measles.

Q And Bilt stands for?

A Bilthoven is a town in Holland where the virus came from. In Chicago 1, it was during the outbreaks in the United States in '89 to '91. That was a wild-type virus that was isolated then, but subsequently has been adapted to grow in tissue culture. Bilthoven we can only grow in cord blood, mononuclear cells. If we grow it in anything else it becomes attenuated. It loses its ability to cause disease.

Q You talked about the receptors. Can you predict based on what you know about the differences that you talked about between the wild-type and the vaccine type, can you predict sort of differences in

clinical presentation or immune response?

A Well --

Q Between the two.

A The vaccine strength generally doesn't cause disease. And we're also inoculating it subcutaneously and the natural infection is obviously coming in by the respiratory route. There's no evidence of transmission of the vaccine virus from one person to another, in contrast to the polio virus vaccine or something, other live virus vaccines sometimes are transmissible from one individual to another. But that's never been demonstrated for measles, and it's probably just because it doesn't replicate in the respiratory tract very well.

Even for wild-type measles, all the major respiratory infection is occurring during that period of disease rash, even though it comes in through the respiratory tract it has to actually circulate back to really get a lot of virus production in the respiratory tract itself. For that person, the person doesn't become infectious for another individual until that, just a few days before the rash onset.

Q Would you expect the complications of wild virus to be the same as those you'd seen in vaccine virus based on the differences you've observed?

A I certainly wouldn't think that you'd see anything with the vaccine virus that you hadn't seen with the wild-type virus. As a recognized complication of wild-type measles.

But I think you would expect that the complications would be dramatically diminished, and we know that, for the vaccine virus. There is no clinically important immunosuppression that occurs, no increased susceptibility to other infections, so the manifestations, a small percentage of children, and the child with one of them got a rash after measles vaccine, so that's maybe ten percent of people will get a rash. Most children get some fever actually, and it's again, five to fifteen percent that get a fever of 103 or more. So to get a fever that would be considered significant. But still that's a small proportion, but it's also a large proportion of people who, of children who get a rash and fever, this particular, with the current vaccine. But as I say, the important components of measles and the complications of measles don't occur with the vaccine.

Q One of the components that's had a lot of focus here of at least the wild viruses, immunosuppression, we talked about that. Do you see that immunosuppression with the vaccine virus?

A As I mentioned, you don't see clinically relevant immunosuppression. Immunosuppression in wild-type measles, the reason that we focus on it is because of this increased susceptibility to other infections. That's why it's important. It's not important because you lose skin test responses or because your lymphocytes don't proliferate very well in vitro, and there's lots of laboratory manifestations of the immunosuppressant during wild-type measles.

If you take the lymphocytes of somebody who has been vaccinated with the measles vaccine and then look for any laboratory evidence of changes in the lymphocytes that are circulating, you could find those. They're not nearly sa profound or as easily found or as reproducible as they are in the wild-type disease. But you're inducing an immune response. That's the reason to give a vaccine, is to induce an immune response to measles. So that's happening and you can document that by looking at the changes in the cells that are occurring or present in the blood.

Q Do you see an increased susceptibility to infection after vaccine?

A No, there's no evidence of that and that's been looked for quite carefully in quite a few studies

to try to look and see if there is any increased susceptibility to other infections. No study has found that. There's just no clinically important, there's not really immunosuppression in a meaningful way that occurs with the vaccine, put it that way.

Q Does the vaccine virus, the immunosuppression that goes along with it, seem to impede the body from clearing the vaccine virus?

A No. As I say, I wouldn't call what the vaccine does immunosuppression. Again, it depends on how you're going to define the term, but there are some immunologic changes that occur coincident with the vaccinations, which are also coincident with inducing the immune response to measles.

Q Turning to the specific facts of this case, on December 29, 1995 Michelle Cedillo received an MMR vaccine. From what you've seen, is there any evidence that she mounted a normal immune response to that vaccine?

A There are a couple of pieces of evidence. First of all, she got a fever and a rash which is a manifestation of the immune response. But more importantly, she got an IgG response which was still present at least two years later which is when it was looked for, which means she established this memory

immune response which requires both CD4 cells and antibody as a part of that memory response, and if you don't get a good immune response to the measles vaccine the usual evidence for that is lack of antibody response of lack of an IgG response to the vaccine.

Q I take it from what you just said that the fever and the rash that Michelle had about seven days afterwards, you're attributing to the vaccine?

A I think that makes a lot of sense. There's no way to be sure.

Q There's been an assertion that measles virus in the gut could attach to monocytes or macrophages in the blood and enter the brain?

A I don't understand how that is going to happen. There's basically, there's antibodies present which is going to prevent the virus moving from one cell to another. That's an antibody's job is to neutralize that virus from infection. The thought that it would attach to the outside of a cell and then move into the brain, I guess I just don't see why that would be happening.

Q There's a claim in this case that the vaccine strain, measles virus, was able to persist. One piece of evidence that's being looked at is what

is purported to be the recovery of measles virus RNA by way of PCR testing, from a gut biopsy sample.

I know you've discussed PCR, your own concerns about the PCR testing in your report on page seven, and I don't want to go back through that because the Court has already heard a lot of testimony on PCR.

What I'd like you to focus on is one aspect of the PCR test result in this particular case that I think you had some concerns about, and that is the copy numbers. What is the significance of copy numbers in the Unigenetics test results to you?

A The only shred of evidence as far as I can tell that measles would have anything to do with this child's disease is that one piece of PCR data. That has to be looked at carefully. As you already said, there's already been plenty of testimony, which I wasn't here for, but I've heard about, that would call into question the laboratory and the data, et cetera.

In addition what leaps out at me is that it's not a biologically plausible number. That many copy numbers of a virus in the amount in the tissue that they looked at would mean that it would have to be an overwhelming infection. It would have to be more virus replicating in that piece of

gastrointestinal tissue that was biopsied than is present at the peak of wild-type measles virus infection.

The fact that there's no pathology that's similar to measles. I mean measles pathology is very characteristic. It causes syncytia, it causes inclusion body formation, it would cause inflammation. There are a lot of things you would expect to see if you have that much measles virus infection in a piece of tissue.

To me, that just wasn't a biologically plausible number and would be one that would be called into question. I'd like to see a repeat, or to know that they were able to amplify it. If they had that much virus they ought to be able to easily amplify it from other portions of the genome, not just that one primer set that worked. If you have a lot then there's no problem with being able to, frankly you probably ought to be able to isolate it and grow it. But most people don't try to do that. But you ought to be able to stain for it, you ought to be able to see it making protein if there's all that much virus. You ought to be able to see it by lots of different ways than just a PCR number.

Q Would you expect to see it in other places?

A I can't imagine why in the world it would only be in the gut, but yes. If you have that much virus in one place it's hard to imagine why it would be only in that one little spot.

Q I know measles, we've already heard testimony, measles virus is known to persist on occasion in humans. Can you describe what happens when measles virus persists in a human?

A Yes. There are well characterized diseases that are associated with measles virus persistence, so there's no doubt that that can happen. The most classic example is subacute sclerosing panencephalitis, SSPE, but there's also -- well, we'll discuss SSPE first. That's wild-type measles that does that.

Q It's not known to occur with vaccine virus?

A No, in fact all cases of SSPE for which there has been suspicion that it has been caused by the vaccine virus have all been proved to have been caused by the wild-type virus.

In that case what I think happens, we don't really know because SSPE occurs 7 to 10, the clinical symptoms of SSPE occur 7 to 10 years after the measles virus infection, and it's a relatively uncommon complication, maybe 1 in 10,000 children. And it's

mainly children that got there wild-type measles infection at a very young age. So most of the cases are children, when people can document when they got their measles, they were less than two at the time they got the wild-type infection.

Then they're normal, or apparently normal, for year until there start to be some usually deterioration in school performance and that sort of thing or some other first signs or symptoms of the disease. And at that time when the persistent infection which is in the nervous system is diagnosed, it's very widespread.

So my assumption of the pathogenesis, and as I say, we never are able to look, we don't have any animal models for this and we can't identify these kids at the time they get their infection and then find out what's happening, is that the virus probably enters the brain in those children at the time of the original infection. Again, often these children are said to have had mild measles, so you wonder whether they mounted a really appropriate immune response at that time. Then the virus, it must just replicate very slowly and spread very slowly through the nervous system through all those years and eventually the thought is it builds up to a threshold that is enough

damage and enough virus replication that there are some symptoms.

Once that occurs, as I say, the virus is very widespread and essentially all of those children die, usually within a year or two of the onset of the neurologic symptoms.

Q What are, you mentioned some intellectual deterioration. What are the other --

A Intellectual deterioration. There are movement disorders. One thing that's known as myoclonus is a common one. They eventually become mute and bedridden. Really pretty profound and progressive change over that period of time. There's characteristic EEG abnormalities, what they call birth suppression pattern. So one of the ways of trying to diagnose it is that way. Another way to diagnose it is they often have very very high levels of antibody in the cerebrospinal fluid indicating that they're making an immune response locally to the virus that's present in the nervous system. Those are all the kinds of things one looks for.

The imaging CTs or MRIs show big ventricles, shrinking brain, basically.

Q Necrosis?

A Well, yes. You're getting cell death

presumably due to the infection, the widespread infection that's in the brain. So it's really quite a characteristic picture which fortunately has essentially disappeared from the U.S. with immunization. We basically don't see this diseases any more.

Q The course of the neurologic symptoms you're talking about from the onset to the end point was about a year?

A It's a year to two years. There are occasional heroic medical care, et cetera. There are occasional individuals who survive longer than that, but that's the usual picture.

Q Does the condition ever not result in death?

A I don't know of any case reports where that is the case, where there wasn't eventually death. As you can imagine during the time, and there are many parts of the world where this remains a very important neurologic disease. Turkey happens to be a particularly good example. They have clinicians who are interested in studying it. So there have been a lot of clinical trials to try to treat the disease with riboviron or interferon or different things to try to intervene, but these are all anecdotal case reports, and since the duration of the disease is very

variable, knowing whether your intervention actually helped or not isn't clear.

There are certainly case reports that the children did better for a while with these treatments. I don't know of any cases of recovery where there hasn't been some sort of antiviral treatment that is, as I say, not recovery but improvement of some variety. I think it's only ever occurred in the face of some sort of antiviral intervention.

Q Recovery, was the recovery sufficient to --

A As I say, it's usually a slowing of the downhill course is usually the kinds of things that are being described. The person quite deteriorating as fast as they had been before.

Q Pathologically, what's happening with the cells here? What changes would we see at that level?

A As I mentioned, there's very widespread infection, either when you do a biopsy because some of these children do get diagnosed by brain biopsy. Others you see an autopsy. But there's very characteristic inclusion body formation that you see in the infected cells in the nervous system. And as I say, if you stain for virus antigens, it's everywhere. This is not hard to find, let's put it that way.

Q When you do these biopsies have you seen any

preferential effect of the measles virus on astrocytes or microglia?

A It affects both neurons and the glial cells, so both are affected. I think that most of the deterioration is due to death of neurons. That's what's really causing the neurologic deterioration.

Q It's actually cell death in neurons.

A Yes. I'm sure even the ones that are still alive aren't functioning too well with all this measles virus in them. You can stay alive and not do so well.

Q You mentioned, what was SSPE and I don't want to cut you short if there's anything more on SSPE, but there was another instance of persistent measles virus?

A The other places it can persist, and this is, or the other situations in which it can persist. So that's, as far as we know, are normal children that have gotten measles and then get this very prolonged --

Q The wild measles?

A The wild measles, and then with SSPE.

There's another whole group of people who get, again, mostly children, that can get measles and develop a persistent infection. Those are children

that are immune compromised. There are numerous reports in the literature that immune compromised may be because they have cancer, or because they have a congenital immunodeficiency or because they have HIV infection. There's a wide range of ways that you can have an immunocompromised individual who then gets measles.

When that happens, again, this is the category of person that may not develop a rash, they basically don't mount an adequate immune response because it's usually, it's almost always children that have a deficit in cellular immunity. They may have a deficit in both cellular and humoral or antibody immunity but usually it's cellular immunity. Those children --

Q I'm sorry. What magnitude of immune depression or suppression --

A This is profound. This is profound immune depression.

As I say, somebody that might be on chemotherapy or may have a lymphoma or have late stage HIV infection. so this is pretty profound immunosuppression.

Those individuals can develop progressive measles virus disease which usually manifests itself

within, usually within months. So the virus again replicates relatively, or it causes its disease over sort of a slow course, but it's a slow course over months. So the most common presentation, they can present either with neurologic disease and neurologic deterioration, or with pulmonary disease and a giant cell pneumonia, so respiratory problems. Those again are progressive. Those all end in death and usually appear, as I say within weeks to months after the exposure to measles or the recognized exposure to wild-type measles.

Q So this is much more rapid than SSPE?

A Oh, much. Much. Yes.

Q And you touched on the immune suppression and the level of it, in this case do you see any evidence, it's been postulated there's an immune suppression. Do you see any evidence of immune suppression of the nature that you're talking about in these measle inclusion body cases?

A No. At least during the first year of life, or whole history, there's really not been an increased susceptibility to other infections. Usually these children are susceptible to multiple infections. And certainly the congenital immunodeficiency ones or the HIV invested ones, have had other infections along the

way. Measles, even measles vaccine is contraindicated in a child with congenital immune suppression.

But I didn't see any evidence in her history that she -- and she got some other live virus vaccines. She got a polio vaccine, for instance. So no indication that she had any problems with any of those. In fact she mounted perfectly appropriate immune responses to the vaccines that she received.

Q You mean these other ones?

A The other ones. If you looked at polio or whatever.

Q Just to take a little aside here, you talked about HIV. I think there's been some evidence introduced about HIV patients who received measles vaccine virus and how long it would take for them to clear the measles vaccine virus. Are you familiar with any of those studies?

A We've done a lot of studies on clearance, per se, of the vaccine. We've done a lot of studies on the induction of the immune responses to the vaccine. I'm mixing up measles virus, the wild-type, and vaccine.

If you talk about vaccine virus, there's at least one case, and I'm sure there are, I know there's more than one, but the one that alerted everybody was

a college student who actually got reimmunized with measles vaccine at a time, and he was HIV infected. This was before we the good antiretroviral therapy that we have now. He basically had AIDS. He had a very low CD4 T cell count. But it was almost a year, during the subsequent year he developed progressive respiratory symptoms and eventually died of a pneumonitis and at autopsy it was due to measles vaccine virus.

So over that year he was unable to clear the virus that he was immunized with.

There are other cases of HIV infected individuals who got the vaccine -- when they're very profoundly immunosuppressed, that then developed a progressive disease.

However, because wild-type measles is such a severe disease in HIV infected children, it is generally recommended that children receive the measles virus vaccine even though they're HIV infected. In Africa they give it even at a younger age. They try to move the age down to six or nine months, mainly because the immune suppression for HIV is progressive over time. The thought is if you can immunize them while their immune systems are still in fairly good shape you'll get a good response to the

vaccine and you won't get any complications.

Q In these individuals that you're talking about, I understand the neurologic outcome was death ultimately.

A Right. So was the respiratory outcome usually.

Q Did you ever see a neurologic outcome of autism in these cases?

A No, that's never been reported. And I haven't seen it, no.

Q That's true either with the wild virus and the vaccine virus?

A No. Autism was not a recognized complication. There's neurologic complications, but none of them are autism for wild-type virus.

Q Do you believe that in this case the MMR vaccine more likely than not caused Michelle's autism?

A No. I think there's no evidence that it did.

Q The pathogenesis that was proposed here that measles vaccine virus persists, it replicates and causes diseases in both the gut and the brain, is there biologic plausibility to this pathogenesis that's been laid out?

A I don't think so. I really do not see how

you can put all this together. There's no evidence that she has measles virus infection in the brain by any of the criteria that we'd like to look at. First of all, perfectly normal EEGs. An EEG shows slowing which is not a characteristic feature of measles virus infection of the brain, a normal imaging, not a progressive neurologic disease, a pretty stable deficit that's been there for --

Q Just to take a step back into something a little more general. In general, a proposed pathogenesis where measles vaccine virus persists, this is the proposed pathogenesis. It persists, it replicates, enters the brain, and causes autism. Do you see biologic plausibility from what you understand of measles virus, both vaccine or wild, for that postulate?

A That is -- I mean --

Q Now causal autism we talked about --

A We know a lot about what measles virus does when it gets in the brain and none of it is autism, and none of the things we know about does she have. So we know what measles virus looks like.

Q Taking a step back to this case with something more general because the Court also needs to have evidence here for something to apply to other

cases.

A Sure.

Q The basic pathogenesis that's postulated in terms of vaccine virus causing measles that persist, enters the brain, and causes autism. Do you see biologic plausibility for that?

A I do not.

Q What's the worldwide mortality for measles virus?

A It remains the second most common cause of vaccine preventable death in children worldwide. It's almost 500,000, 450,000 I think is the current estimated numbers of deaths that are occurring worldwide due to measles.

We forget in the U.S. what a serious disease it was and why it was such an early target for the development of a vaccine, because the morality is substantial. And the mortality is substantial, even in developed countries. It's less in developed countries, but it's substantial. And if everybody gets it, that's a lot.

Q Thank you.

MR. MATANOSKI: I have no further questions at this time.

SPECIAL MASTER HASTINGS: Let me ask both

counsel, is it your preference that we go ahead and finish with Dr. Griffin tonight?

MR. MATANOSKI: It's certainly the government's given Dr. Griffin's schedule.

SPECIAL MASTER HASTINGS: All right.

Ms. Chin-Caplan, do you want to go ahead?

MS. CHIN-CAPLAN: Sure.

CROSS-EXAMINATION

BY MS. CHIN-CAPLAN:

Q Good afternoon, Doctor.

A Hi.

Q Doctor, you have these slides that you presented to the Court. Would it be fair to state from the slides that you presented that the period of maximum viremia coincides with the period of immunosuppression?

A No. Immunosuppression lasts for a much longer period. This little graph really only shows the acute phase of measles. You can detect these changes in immune responses, these increases of susceptibility other infection during the acute phase, but actually it continues for three or four months after that.

Q My question was actually a little more basic than that. From what we see on page four here, it

seems that the period of maximum viremia which is somewhere between I think it said 9 and 14 to 15 days, is also the timeframe when one starts to see immunosuppression?

A Yes, you may even be able to see it before that.

Q It's just not clinically evident at that time, correct?

A It can be. The time that children are getting their secondary infections is often during this period of the rash and shortly thereafter that these complications of pneumonia and that sort of thing occur.

As I say, it's a very paradoxical thing because they're making a wonderful immune response to measles and clearing of measles, but it's these other infections that they're more susceptible to.

Q You indicated also that the period of immunosuppression lasts longer than the period of maximum viremia.

A In the wild-type disease it does. In vaccine, as I say there's no immunosuppression really in vaccine disease, but any immunologic abnormalities that you can find are more confined, put it that way.

Q For the wild type, how long does the period

of immunosuppression last?

A We've looked out, I guess it depends on how you're going to actually define it, but there's increased susceptibility to other infections certainly for a couple of months after apparent recovery.

Q You indicate that increased susceptibility for infections were a couple of months after what timeframe?

A After the clearance of the rash.

Q So roughly when the rash appears, about seven days afterwards, the individual would still be susceptible to infections for a period of two months afterwards?

A Obviously it's varying from individual to individual, but if you look at -- I think anybody that's going to count measles and measles-related deaths will often, which as I say are mostly due to other infections, is usually in that two to three month time period from the time of measles rash, or recognition of measles.

Q Does the immune system still demonstrate some sort of abnormalities when it's measured after that timeframe?

A After the three months or so?

Q Yes.

A We've not, I'm trying to think of what kinds of studies. I suppose it depends on what you mean by abnormalities. And if you're looking at skin test responses, so a loss of the tuberculin response which is common by the time of the rash. That takes about a month before that comes back. Four to five weeks before that's normal again.

So different parameters are going to be different over different timeframes. As I say, we mostly are concerned with this increased susceptibility to other infections.

During all this normal, what was really a normal immune response to measles, you have a lot of changes in cells that are occurring and the kinds of cytokines they're making, et cetera. Those things gradually change over time.

We've certainly followed children out for three months is usually about as long as you can usually get parents to bring back children after they've recovered from measles if you're going to do a study. So you still may be able to find some cytokines that are high at that point compared to control children. So it's a gradual sort of going back to what you might consider a baseline after making this immune response.

Q So there's a gradual return to baseline after approximately three months, but you indicated that you still see things like elevated cytokines present for longer --

A In an occasional child you could. But three months is sort of the outer limit. But I won't say that if you looked at five or six -- Most studies stop at a month, but we've carried studies out for three months.

Q The elevated cytokines that you see, what type of cytokines are they?

A We didn't really go into all these different things that are happening with the immune system during that period of time. But -- Can you put that one back up? I guess you just need -- yes, that one.

If you look at the CD8 T cell response on the bottom, that's a very up and down during the rash. And again, all of this is looking at what's going on in the blood because that's what we can sample.

So CD8 T cells are greatly expanded and then they're quickly brought back. Those are the cells that are probably most responsible for clearing the virus in that top graph. They actually can kill cells that have a virus infection. But if you look --

MR. MATANOSKI: This is Slide 4.

THE WITNESS: Excuse me. Yes.

But CD4 cells have a much more complicated role in -- I mean CD8 T cells also produce cytokines, but CD4 cells have been most thoroughly studied and their main job is to produce cytokines.

So early on during sort of that same time you're seeing an elevated CD8 T cell response, you're seeing what we call, and I know it's been discussed here before, but a Type 1 CD-4, a T-Helper-1 type of response and T-Helper-1 cytokines that are being produced -- interferon gamma, IL2 are produced during this acute phase.

Then those get, as I say, one of those things that have to happen is you have to shut down all of those cells so you can put things -- You have to do two things. First of all, you want to mature that antibody response, so that's another job of CD4 T cells. The ones that are most important for producing the cytokines that are most important for the antibody response are the TH2 cells.

Those are producing cytokines like IL4, IL13. There's another group of cells which are called regulatory T cells which are probably the ones that are helping to calm things down, bring things back down more closer to baseline which produce IL10.

We could measure, so those cytokines tend to, there's a shift over to the TH2 type of an immune response which makes an awful lot of sense. First of all, you need to mature those B cells in the best possible way for long term protection, and you also need to dampen down that acute immune response. So both the regulation and the B cell maturation are things that are happening really after apparently there is recovery from the infection. So it's all a totally normal response to measles. But it involves all these different normally produced cytokines.

Q So when the period of immunosuppression begins, is there a skewing towards TH2?

A The immune suppression really start before that, but it can still be present during that time, and that skewing may have some role in the immunosuppression. As I say, immunosuppression, a lot of us have studied it and it's a very complicated process. We don't fully understand it. But certainly one of the jobs of the CH2 cytokines is to down-regulate, macrophage activation, and down-regulate the type 1 T cell response. That type 1 T cell response may be important for another, if another virus came along. That may be one of the reasons that there's an increased susceptibility and it's certainly one of the

hypotheses that we have out there. I don't think it's the whole story. There are other hypotheses, that there are just not enough cells, the cells get killed off, that kind of thing, but those are pretty transient.

Q When you have a TH2 skewing, is that an indication that should the body encounter another pathogen that it might not be able to clear it as well?

A It's hard to know. It depends on what that pathogen would be. As I say, we don't have a good understanding of how much that TH2 response is contributing to the immune suppression, per se, and the increased susceptibility to other infections versus just being totally a normal response.

Those studies are basically impossible to do. There's no way to challenge somebody and do a comparison of whether they got infected or didn't get infected. Those were the kinds of studies that we were doing in Peru, trying to look at children who got pneumonia and other complications versus the neurologic disease, versus they had no complications at all. From this point of view they all looked the same. That suggests that maybe there's something else that is really accounting for that increased

susceptibility to other infections, and it may be something as simple as one of the places a virus replicates is in the respiratory tract. If you have damage to the respirator tract then, as I say pneumonia is the most common complication, that you fend off respiratory pathogens less effectively.

So I don't think we really have a good understanding of how these various things relate. We can describe what's there, but ascribing any one of them to the actual increased susceptibility to other infections is difficult.

Q Wouldn't it be fair to state that with TH2 skewing there's less TH1 to clear viral infections?

A TH1 cells are not what clear this virus infection, and it doesn't mean that you can't induce those TH1 cells if another virus infection comes along. So measles induced is a perfectly good TH1 response, and then the later phase shifts, basically the TH1 to TH2 shift occurs.

This may be common for many virus infections. For whatever reason, people have really, for acute virus infections people have really only studied measles. That's probably because we're studying measles.

We know that this increased substitutability

to other infections occurs with a lot of other viral infections. Chicken pox is a good example. Influenza is another good example.

So there are lots of viral infections, but the real complications are secondary infections, other infections that occur, not the original infection. So I think there's a lot of ways that a virus can make you more susceptible to other infections and their may be something common between them or they may be different.

Q It's fairly well known that viruses can cause immunosuppression and make people more susceptible to opportunistic organisms, correct?

A Yes, some virus infections. It varies on how important that is clinically, but wild-type infections, I don't think there's any evidence for any vaccines that that happens.

Q You edited the chapter on measles in "Fields Virology" I think you said.

A I wrote it.

Q I'm sorry. You are the editor and you wrote the chapter, correct?

A True.

Q Doctor, in that chapter you also included a section on measles vaccine, didn't you?

A I would hope so.

Q I'm looking at an exhibit in Dr. Fujinami's which is Respondent's Exhibit R, Tab 17.

Doctor, it looks like Chapter 44 from "Fields Virology," is that it? Measles Virus.

A I can't see it.

(Pause.)

A Right, but I don't know if this is the current edition or not.

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, did you say Tab 17 to Dr. Fujinami's?

MS. CHIN-CAPLAN: Eighteen.

BY MS. CHIN-CAPLAN:

Q Doctor, you have a section on attenuated live virus vaccine.

MS. CHIN-CAPLAN: You don't have it for the Doctor, do you?

MR. MATANOSKI: No. We don't have a copy.

(Pause.)

THE WITNESS: 1427 is in the references, is that correct?

BY MS. CHIN-CAPLAN:

Q It's the page I have here. It says attenuated live virus vaccines on the left hand column.

SPECIAL MASTER HASTINGS: Can you speak up?

THE WITNESS: I cant' read it.

BY MS. CHIN-CAPLAN:

Q It says attenuated live virus vaccine --

A I can't read it.

Q Okay.

Doctor, I'm going to refer you over to the right-hand column, and the next to the last paragraph. It says "Administration of standard dosage of live attenuated measles virus vaccine results in transient lymphopenia." What does that mean?

A That means a decrease in the number of lymphocytes that are circulating.

Q Would that affect ones ability to fight off infection?

A Not that we recognize.

Q So clinically you're saying it doesn't appear to cause any harm.

A There is absolutely no evidence that it does clinically. We can measure a number of changes. And a lymphopenia is probably due, at least our understanding of that, is probably due to change in circulation of the cells because as I say, all of this induction of the immune response is going on in the lymph nodes. The cells that are running around in the

blood, which is what you're measuring for lymphopenia are not useful from that point of view until they get their instructions and get expanded in the lymph nodes. Then they come back out.

So during the time of the induction of the immune response, and this happened within wild-type measles as well, it was much more profound than it is in vaccine. You see the transient drip which is probably due to the cells getting the signal that the best place to be is in the lymphoid tissue participating in the induction of the immune response, and then they come back out.

I think it's most likely this is a trafficking, it's not a real change in the number of lymphocytes, there's a change of where they are at any one time.

Q Would that be the same thing for wild-type?

A For the wild-type, as I say, it's a much more profound change that occurs really during that rash phase. Again, during that immune response, intense immune response phase. So it's one of the things that's happening during the immune response.

Q It's an attenuated version of what would occur in wild-type, is that it?

A This lymphopenia?

Q Yes.

A Yes.

Q The suppression of delay type hypersensitive skin test responses to recall antigens, what exactly does that mean?

A Those are the tuberculin tests for the most part. Those have been documented to be -- Mostly those papers are fairly, were with the original vaccine. It went through a stage of the original vaccine and then a more attenuated version, which is our current strain, moratin, that causes less of that. I'd have to see what the references actually are, but a lot of them are early vaccine references. But there was that documentation.

Q When it says that you lose the tuberculin test result, is that it?

A Yes, you can. Again, it's not clear that that happens with the current vaccine. Put it that way.

Q But in the earlier vaccines it was --

A Attenuated vaccine, right.

Q This ultracytokine production. Are these the cytokines that you were referring to earlier? The IL4?

A Yes. And again, those are seen, I think

studies have been done more and more. You see those mainly, in fact if you look at a number of our publications, we're looking at individuals who are being revaccinated. So right now we give two doses of the vaccine. In outbreak situations like occurred in '89, '91, we gave a second dose, we sort of reimmunized all the people working in the hospital, for instance, because of the outbreak.

I don't know why this is. I assume it's because you're inducing that memory response that you see actually more of these cytokines that were sort of like what you could see in wild-type. So you see the IL4, et cetera. You can see those induced as a part of the memory response. Again, it's a manifestation of the fact that the T cells are there, the memory T cells are there. They've helped the B cells and the kind of memory T cells that you have are those same variety that were induced during the acute response.

The basic immune response, just as a matter of greatly attenuated degree. I mean the amount of antibody you get in response to vaccine is about ten-fold lower than you get in response to wild-type infections. So there's a lot of matter of degree here. It all adds up to it's not a clinically relevant, but you can definitely identify changes that

are occurring as a part of the induction of the immune response to the vaccine.

Q And the changes that were listed in your chapter here, they're the same changes that you see in wild-type except to a lesser degree. Is that what you're saying?

A Fundamentally. We've only looked at a few cytokines. In fact we haven't looked at IL10 really at all, which we've looked at in wild-type disease. But certainly if you look at the characteristic, interferon gamma IL4, yes, they are similar.

Q And interferon gamma is a TH1 response, correct?

A And a CD8 response.

Q You need interferon gamma to clear infection, correct?

A Not necessarily. You need to be able to induce -- infections vary. What you require. It's one thing to say the memory response to measles is IL4 and not interferon gamma. It's an entirely different thing than saying what's the response to a new virus where you're going to go through this whole scheme again, to induce the CD8, the CD4, to this new batch of antigens and virus antigens and that sort of thing. There's no reason to think that's not going to happen

in a perfectly normal way even though the memory response to measles, per se, is still that memory response to measles.

Q And yo in fact have actually done some cytokine work with Dr. Ward, correct?

A Right.

Q That was you measured IL4 after vaccine?

A Those were in the hospital workers who were being revaccinated. So as I said, we were really looking at the memory response.

We've done studies subsequently in babies who are being, not with Brian, but I've done some studies subsequently in babies that are being immunized with MMR or with just measles alone, and we really can't find those changes in the primary response. So they may just be much easier to see as a recall response.

Q So it the opinion now that you only see it as a secondary response in somebody that's already been exposed previously?

A It's certainly more profound. It's a different sort of memory response, it's more easily seen for a memory response probably because you already have a fair number of those cells than it is in the primary response. But as I say, I still stink

the same thing in miniature is going on in the primary response. But since we can only measure what's going on in the blood, and when you're talking about immunizing infants and studying them you're very restricted in the number of cells, how often you can actually look at the responses, et cetera. So those studies are just much harder to do and most people haven't done them.

Q When you did your IL4 study with Dr. Ward, you indicated it was in hospital workers, correct?

A Yes.

Q You only went out about 14 days after the immunization? Is that it?

A I think so. I'd have to relook at the paper to, but yes. I don't remember how long we went out.

Q It wasn't a long-term follow-up.

A No. It may have been three weeks, but --

Q Okay.

Doctor, we had talked earlier about your Slide 4, and you know that Michelle Cedillo had a temperature of 105, almost 106 at approximately seven days out after measles immunization. If one looks at your chart that seems to coincide with the period of maximum viremia.

A I think she had a rash at the same time,

didn't she?

Q I don't recall. I remember the fever.

A Okay.

Q But the fever would be occurring at the time of maximum viremia, wouldn't it?

A I don't know if it's going to be, or maximum immune response.

Q Maximum immune response. Okay.

A But the immune response is being induced in response to the virus. These things, as you can see from this chart, are all happening at the same time.

Q Yes. So would it be fair to state that the fever was probably related to her MMR?

A I think it probably was, yes.

Q We do know that that fever subsided for a period and it recurred. It recurred at approximately 16 days out. She had the fever for about four days, then it went away for a few days then it came back. Do you believe that second fever is also related to the MMR?

A I would doubt that. Children get fevers due to a lot of different things especially at that age. I would not think that was, a biphasic response, as far as I know, with measles vaccine or with measles.

Q But that would still be within the period of

immunosuppression that you've documented --

A But right here you're looking at wild-type virus. You're not looking at vaccine. And there's one major difference is that you get a very small amount, for wild-type virus you get a very small amount of virus that you breathe in, and then it takes all those days of seven, eight, nine, ten days to build up to the amount of virus and induce the immune response, et cetera.

With a vaccine virus you're inoculating a fairly, thousand plaque forming units, infectious units, subcutaneously, so you're bypassing all that early stage.

I'm just saying the vaccine response is earlier. It's skewed, so to speak, to be earlier than you

see with wild-type virus where you have to go through a phase of a lot of virus replication to even get to the point that you have as much virus as you put in for the vaccine to induce the immune response, and you have to do that with a vaccine because it's not going to replicate as well, you need to sort of get a head start.

So I think for the vaccine usually it's around seven to ten days, five to ten days is the

usual time period that you see the complications, the rash, fever, et cetera, due to the vaccine, and those have been pretty well studied.

I think 16 days would be quite a ways out from what the observed, or what I would expect with the vaccine virus causing a fever per se.

Q Do you know whether IOM has indicated that reactions occurring from 5 to 15 days would be considered to be related to the measles?

A Usually they give a fairly broad range. So 16 days is outside their 15 days, but --

Q If they say 15 days and it occurred at 16 days, you really wouldn't quibble that much about the day, would you?

A I don't know. I just think that this biphasic, the fact that she already had something that makes sense that it was related to measles vaccine would suggest that the second fever was due to something else.

Q Their was also testimony that Michelle suffered diarrhea about two weeks after the immunization. In your opinion, would that be related to the MMR?

A I wouldn't know any reason to think it was. As I say, there's been lots of pretty extensive

studies looking for any kind of infectious complications that occur as a consequence of vaccination, of MMR specifically. I have no way to know. I don't know how much she was worked up or people tried to figure that out, or if she was even seen.

Q So when they say that measles is enterotropic, what exactly does that mean?

A I wouldn't san measles was enterotropic.

Q No?

A No. Measles is lymphotropic. It replicates again, it replicates in lymphoid tissue everywhere. It's in the appendix, it's in the spleen, it's in the lymph nodes, it's in the tonsils, it's in the sinus. You look at any lymphoid tissue and it's infected.

In addition to that it can be found in a lot of other, and a lot of gut lymphoid tissue. As I say, the appendix is a well recognized site for it to replicate and I'm sure it probably replicates in the other lymphoid tissue as well.

But it doesn't have any special predilection to replicate in the gut or certainly the gut mucosa. In contrast to an enterovirus or something where that's the main site of the virus replication.

Q But it's definitely neurotropic, correct?

A It's neurotropic not in this type of sense. It can cause neurologic disease that we've already talked about which are very characteristic diseases, SSPE, measles inclusion-body encephalitis where again you see the same kind of pathologic picture and a very characteristic clinical picture. So there's no doubt in those special situations of where you have this infection at a very early age that then leads to this SSPE 7 to 10 years later, or this infection in the face of profound immunosuppression, frankly, that it can get into the nervous system. That's true.

It's interesting that the virus that's present in the nervous system is quite heavily mutated compared to the original virus. So it sounds like, it looks like, and again we don't have any way to really do these studies, but it looks like for the virus to be able to be in the nervous system requires these mutations and these mutations actually alter the ability of the immune system to see the virus.

Q Would you say that for a virus to persist that there has to be some sort of immune dysfunction?

A Oh, no. There's lots of viruses that persist when they infect people that are originally perfectly normal. I mean HIV is a perfect example. You have Hepatitis C virus. All the herpes viruses

that persist in most of us after, and we're hopefully immunologically normal. So virus persistence is certainly not cause, it doesn't mean you have to be immunosuppressed to have virus persistence.

Q But if a person is immunosuppressed the risk for viral persistence increases, doesn't it?

A Yes, I mean I guess it depends on the kind of immunosuppression. We know that people who are hypogammaglobulinemic, for instance, don't have good antibody responds, actually do pretty well with measles, interestingly enough, but they do badly with polio or some of the other enteroviruses. They do very badly with certain bacteria which really requires antibodies. And while there are other diseases where components of the cellular immune response is much more important for virus clearance and some where the antibody response is the most important. Even some aspects of the innate immune response are important for clearance of herpes viruses. So all these viruses are very, they're wily, they're complicated, and their interactions with the host are complicated. So you can't extrapolate from one to the other very easily. You have to study each one and understand it.

Q And measles is particularly difficult to study as you indicate because it doesn't really occur

in little rodents, correct?

A It's a human virus, yes, but there's been a lot of human studies and there have been a lot of monkey studies that are going on. so you can do it. It's not as easy as infecting a mouse, that's true. It also may not be as relevant.

Q You have to use monkeys primarily to study the measles virus, don't you?

A We do a lot of human studies, too. We study both people and monkeys.

Q But if you wanted to see viral persistence, you would probably test it in a monkey as opposed to a human?

A Well, we've done a couple of studies in Zambian children following virus clearance. I think it's really a question, if you look on the top of the graph, that curve represents ability to recover infectious virus. So if you try to grow virus, that's what that curve looks like.

However, if you do PCR on those same individuals in that graph, you can find virus for a much longer period of time by RT-PCR. it's much more sensitive. It takes a while to get rid of all of the cells that were ever infected. There's no longer any spread of the virus. But the process of virus

clearance as we have more and more sensitive techniques, it's not as straightforward as most people would hope I guess. The dogma is that, that curve is the dogma that once you get that infectious virus you're not going to be able to, that all the virus is gone. But we know from studies, a number of different kinds of studies, that if you do RT-PCR on, it can be urine or nasopharyngeal swabs, or blood in children who have recovered from measles, or monkeys, and we've done it on both monkeys and kids, then it takes actually, well in kids we can still find it at three months. Probably in monkeys we saw it out to six months. So by five to six months, all the virus is gone. But as I say, it just depends on the sensitivity of the technique that you apply to trying to -- Which is probably the reason, the fact that it clear is a prolonged process, it takes a while in wild-type infections, that you continue to see the cytokines and the T cell responses, et cetera, for a period of time after the rash is gone.

As I say, when the rash is gone, the fever's gone, the kid feels fine, but a lot of other things ar still going on with the immune system after that.

Q You've done studies on viral persistence, haven't you?

A Yes.

Q You've indicated that if you used more sensitive techniques that you could find viral persistence for a long period of time and it depends on the type of techniques that you use, correct?

A Yes.

Q You've actually done some experiments on, is it Sindbis virus?

A Sindbis virus, yes.

Q Yes. And I think there's an article you attached at Respondent's Exhibit V, Tab 64. The title of this is "Long-Term Intraparenchymal Ig Secretion After Acute Viral Encephalitis in Mice."

Doctor, I'm going to have your counsel --

A I know the study well.

(Laughter.)

Q It's been a while.

A We're still working on this question.

Q You used PCR technique to detect Sindbis virus RNA in the brain, is that true?

A Yes.

Q And it indicates in the abstract that three months after inoculation 47 percent of the B cells found in brains are secreting antibody specific for Sindbis virus structural protein. Is that true?

A It's true.

Q By a year, 62 percent are Sindbis virus specific. B cells for treating IgG2A predominant.

So even after a year there's still RNA present.

Further on it says, "Preliminary chain reaction data indicate that despite complete clearance of infectious virus by seven days, Sindbis virus RNA is still present in brain at least six months after infection."

A Right. In fact this study, and this is the other kind of virus that we've studied, so this is a virus that infects neurons. That's its main target cells, the way we do these studies, was, and we were very interested as I already indicated, one of our research interests gives virus clearance. And what does the immune system have to do to actually clear virus?

So in this case this virus infects neurons. Neurons are not a population of cells that one can replenish. You lose your neuron, your neuron's gone, you're not going to get a new one. But it's a type of viral encephalitis that these mice can recover from. So you can get acute virus replication that's similar to what I've just shown you from measles, and then you

can't get infectious virus back any more, which frankly is due primarily to the fact that you've got a lot of antibody around, but the mice totally recover.

This is true of humans, too. You can have a viral encephalitis that people get better from totally where they have infected neurons and they don't have long term paralysis or mental retardation or anything else.

In this series of studies that we continue to do on this particular virus that's neuronatropic and affects neurons primarily, what became clear was that the immune response had a noncytologic approach to clearing the virus. So basically to clear all the infectious virus you had a, if you look by PCR, you found a dramatic decrease in the amount of RNA that was present, but it never totally went away. That's because neurons are very special cells. They're cells that don't turn over. As I say, the neurons you get when you're born are pretty much the neurons you're going to have.

Basically what this specialized group of cells, and it's true probably of cardiac cells as well, myocites who don't replace those very well. The best way for the immune system to get rid of a virus is to kill the cell that the virus is in. And if it's

disadvantageous to kill the cell the virus is in, like it's a neuron, then it is very smart for the immune system to figure out another way to be able to control the virus without having to actually kill the cell and get rid of it.

That's what happens. It's sort of peculiar to long-lived cells that can't be replaced. Cells that turn over, so like cells in most of our body and that's certainly true of epithelial cells in the lung or the gut, lymphocytes, all those cells, those populations turn over pretty rapidly. It maybe a month or two months or something like that, but they eventually, there's no ones. You don't have long-lived cells for the most part. Your gastrointestinal epithelial cells are turning over all the time.

If that's where the infection occurs, then fine, kill off the cells. We'll make new ones.

So if you think about influenza, I always think of as a good example, because that's what happens with influenza. You've had influenza, you know the cough can persist for a couple or three weeks, and that's because it's taking that long to get all your new cells growing back and repopulating your respiratory tract.

So the cells that we know that measles virus

infects are all cells that turn over. And so it's certainly true in the gut. A classic example of pretty rapid turnover of cells.

So there isn't this long-lived cell mechanism or problem with measles, and we think most of the clearance is occurring due to cytotoxic T cells, basically, that are actually killing the cells. In many instances the virus infection itself will kill the cell, which is actually a handy dandy way to get rid of an infected cell if the immune system doesn't do it. If that cell dies, even if it's just dying as a part of its normal life span, it normally only lives a couple of months that those cells turn over. So they may be an important component of clearance of some viruses. So the nervous system is a very special example and as I say, I think it's a fascinating biologic problem as to how you control viruses in a cell that you can't afford to get rid of. So that's a reason we're doing those studies. And we have a fair amount of data on how the immune system is doing that. But I don't think it's relevant to measles, frankly.

Q Doctor, in this article, in the abstract, the very last sentence says, "The persistence of Sindbis virus RNA suggests that viral protein may continue to be made providing the impetus for the

continued presence of Sindbis virus specific B cells in the brain."

A Uh huh.

Q In this sentence you're indicating that because you're able to find the RNA that it's --

A No, it's not because of the RNA. It's because we're finding the B cells.

Q The antibodies.

A The B cells in the nervous system. so these are B cells that have gone specifically, so we're looking at B cells in the nervous system. This is not a place B cells normally are, and they're there making antibodies. And so the reasoning there is that the B cells need to be in the place where the viral protein, where the virus is, and that they need to, and that they need to be stimulated by something. Why would they go there and why would they stay there if there wasn't some stimulus for them to keep making the antibody in the nervous system?

The same kind of thing happens in SSPE. It turns out it's not very effective. As I mentioned before, one of the ways that you diagnose SSPE is to look for increased levels of antibody in the CSF. That's because B cells have come into the brain in response to that infection that's there and those

proteins that are being made and are easily detected by immunocytochemical staining or whatever you want to look at. You can find a protein in the brain.

So I think that the B cells are there, the reason we think the protein is there is because the B cells are there. But the RNA itself would not give us any information on whether proteins were being made.

Q Doctor, as I read this it seems like the persistence of the RNA to suggest that viral protein will continue to be made providing the impetus but the continued presence of Sindbis virus specific B cells in the brain. So it's the presence of the RNA that generates the antibody response, is that what you're saying?

A No, the antibody response is not to the RNA. The antibody response is to the proteins.

Q Right, but that's what you said.

A You need RNA to make protein.

Q "The Sindbis virus RNA suggests that viral protein may continue to be made."

A Right, because you can't make protein without RNA.

Q Right. So the presence of the RNA you said suggests that the viral protein is being made.

A It's the presence of the B cells. You have

to have RNA to make protein, and you'll not get B cells, but RNA does not have to make protein. RNA can make protein or not, depending on what it's doing or what kind of RNA it is. But the B cells can only see the protein. So our clue to the fact that the RNA was coding for protein to be made was the fact that B cells were there. You need all three components.

Q Okay. Understood. Doctor, in your opinion, I'll ask that counsel give you a copy of your opinion.

A I have a copy of my opinion.

Q Okay. I just wanted to go through some of this with you. You drafted this opinion before Dr. Bustin was a witness.

A Right.

A You had participated in the U.K. litigation is that true?

A Yes.

Q What was your role in the U.K. litigation?

A Well, similar to here. An expert on measles and immune responses to measles.

Q What knowledge did you have of the laboratory procedures in the O'Leary laboratory?

A I think most of it's privileged information. He may have to advise me. I have a lot of information that came out as a part of that case, much of which is

not public so I don't know what I can tell you.

MR. MATANOSKI: I don't actually think that she would be cleared to talk about what knowledge she would have on the case, Your Honor. Obviously it was Dr. Bustin and Dr. Simmons and Dr. Rema whose reports we obtained.

THE WITNESS: I mean I have those reports and I know what they said, but --

SPECIAL MASTER HASTINGS: Let her ask the question.

MR. MATANOSKI: I think if you want to ask whether what she put in here is dependent on anything she knew from that litigation, I think she could answer that.

MS. CHIN-CAPLAN: And that's exactly what --

BY MS. CHIN-CAPLAN:

Q I wanted to know where the basis of your opinion for, for your criticism of the O'Leary lab comes from.

A I have to see what I actually said here. A lot of it comes from the literature. There's been a lot of public criticism. There have been retractions by the people that published the paper, the Uhlmann paper. Most of those authors have disavowed those conclusions. There's been, actually very early on in

the Wakefield stuff I actually visited the U.K. at his invitation to be a consultant and it was rapidly apparent to me they didn't know how to do PCR. They were in sort of a phase, I think it was before the O'Leary thing. But I was suspicious from just the personal interaction.

But I think that most of what is in here is not from what I learned in the U.K.

Q So the basis for your opinion that, and I'm looking at page eight of your report.

A I didn't number my version here. Okay.

Q You speak of, in the middle of that first paragraph, "any negative for controls was accepted as the result and any positive for patients was accepted as a result, even if other assay runs on the same patient population are giving the opposite result."

Are you referring to a different paper? Are you referring to --

A I'm referring to this example that I gave about the HTLV-1 paper which happened to be a paper I reviewed and tried to prevent being published. So I had a fair amount of knowledge about what the problems were with that paper and it was just a very, and the literature is full of false PCR data. This is just one I happened to know a fair amount about.

Q Okay.

SPECIAL MASTER HASTINGS: Doctor, she asked you, we'll get through this quicker. I think she asked you a very simple question. What paper you were referring to. And now you're telling us about the paper. I think the answer to the question, you answered it already.

THE WITNESS: Okay.

BY MS. CHIN-CAPLAN:

Q Doctor, that next sentence, you say most of these points apply to the way in which the study by Uhlmann, et al was carried out. What points are you referring to?

A I haven't been able to find your spot.

I think it was whether the controls were being done appropriately.

Q The control?

A Right.

Q That was in the Uhlmann paper?

A Right.

Q Anything else?

A I certainly had talked to Atzal, these people in the U.K., people who had tried to, I'm trying to find this.

The sequencing, there was no evidence of

sequencing of the PCR product which was necessary. So those kinds of things were done in this HTLV paper and also were apparent that it was a problem in the Uhlmann paper. I did not base this on knowing all the things in the Bustin report because I did not know those things.

Q Okay. Doctor, I'm just going to ask you because it's not clear to me when you refer to the problems of controls and the sequencing in the Uhlmann paper. If you would just look at Tab 66, Exhibit 66 in your report, attached to your report, can you tell me what is the problem with the control?

A I'm not going to be able to give you a detailed critique of the Uhlmann paper, if that's what you're looking for.

Q 66.

A I don't know what that is.

Q So you can't tell me what the problems with the controls were in the Uhlmann paper?

A It was, unfortunately I don't have the Uhlmann paper in front of me.

(Pause.)

A The biggest problem was they didn't do sequencing of their product.

I don't want to claim to be a PCR expert.

We do PCR. We use a lot of controls.

Q It was the sequencing that you --

A That's the biggest thing, in my opinion. It's the only way you can detect whether you have contamination, the only way you can detect that you have vaccine virus versus wild-type virus. It's just a necessary part of this kind of analysis.

Q So it's really that last step, that sequencing that you objected to the fact that it wasn't done in the paper.

A Right.

Q Doctor, you mentioned Dr. Afzal, you discussed something with Dr. Afzal. What --

A I knew he was doing this study of comparing labs.

Q Comparing labs?

A Yes.

Q So Doctor, would that be --

A And the O'Leary lab didn't participate in that.

Q Right. But there were other labs that didn't participate, isn't that true?

A That did not?

Q Yes.

A Yes, but none of those were putting out a

diagnostic test for measles for autism.

Q Well Doctor, how many labs were invited to participate?

A I'm sure that probably every lab that had ever published on PCR and measles probably was invited to participate.

Q If I told you that there were 13 that were invited to participate, would that sound about right?

A Probably.

Q If I told you that six decided not to join int he study, would that sound about right?

A I can't remember how many.

Q Approximately half decided not to participate.

A Right.

Q Doctor, if I told you that the problem when comparing these laboratories, there was a thousand-fold difference between the laboratories and their results, isn't that true?

A I don't remember the specifics of the paper. There was a difference. There was one laboratory actually that stood out as I recall as being particularly problematic compared to all the others.

Q And their was a thousand-fold difference in sensitivity.

A I don't remember.

Q So if I told you that, you wouldn't dispute that.

And if I told you also that the one lab for which there appeared to be some contamination with FDA, that wouldn't, you wouldn't --

A The lab that I remember had the biggest problem was the Japanese lab.

Q The Kawashima one?

A It was something --

Q And Doctor, if you look on page 175 of Tab 1 of your report, approximately 11 lines down. The sentence says, "Although none of the participating laboratories reported the presence of measles virus nucleic acid in any of the gut samples A through D that were derived from four new cases of Crohn's disease, Laboratory 5 described an ambiguous result from one of these samples. It is reasonable to speculate that the measles virus signal observed in Sample A originated through cross-contamination."

Laboratory 5 is FDA.

A Okay. That's the way we figure out cross-contamination.

Q Okay. Now you also mention in your report that people attempted to replicate Dr. O'Leary's

results and were unsuccessful, and you cited Atzal and D'Souza.

A Uh huh.

Q Doctor, Atzal and D'Souza were tests that were done on blood, is that correct?

A Yes.

Q Mononuclear cells.

A Uh huh.

Q and they were unable to recover any measles RNA is that true?

A Right.

Q And Doctor, we do know that the measles RNA in this case was recovered from gut tissue, is that true?

A If it was recovered.

Q And if it was recovered do we know what the correlation is between the gut tissue and the mononuclear sites?

A I don't think that, for PCR results I'm not sure that is relevant. Cells are cells. It depends on what you're trying to deduce from it. But for the purposes of how you do PCR and how you detect positives, you do it the same for one sample versus another.

Q Wouldn't it be important to try and limit

the variability as much as possible?

A I don't know, it depends on -- I think PBMCs are probably pretty good at limiting the variability. There are ongoing studies to try to look at gut tissue, but there's a lot of problems with biopsying children who don't need to be biopsied, and just to do PCR on their gut tissue.

Q Doctor, don't you think these symptoms that these kids are having are real?

A Oh, I don't doubt that they have symptoms, but there's a lot of reasons to have symptoms, and none of them that I can think of would be measles.

Q When they have symptoms it's reasonable to work up the symptoms, isn't that true?

A Well, yes. If you think this is medically indicated and that you're going to learn something that you're going to be able to do something about by doing that medical procedure, then I guess biopsy is appropriate. But I think that for many of these children that's not thought to be the case.

But I'm not a pediatric gastroenterologist, I'm not an expert on autistic enterocolitis or work up these kinds of kids. I'm outside my territory if you're asking me how you take care of these patients.

Q Doctor, when there's a wild measles

infection you're able to recover that virus from the blood for a period of about seven days after the wild virus has appeared, is that true?

A There's a period of viremia, in wild-type measles the viremia is generally about 9 to 14 days, there's a period. And yes, it may be five to seven days during which you could actually recover the virus.

Q And you're not always able to recover the virus, isn't that true?

A Well you can if you take it at the right time.

Q If you take it at the right time. Right. And even if you take it at the right time, not everybody has been able to recover it, isn't that true?

A I think it depends on what they're using for their recovery technique. Most people don't try to recover measles, frankly. It's not the way you diagnose measles, it's a laboratory procedure, it's a research thing basically to try to recover the virus.

If you culture cells on the first day of rash appropriately I think most people can recover the virus. It becomes steadily less likely with time.

Q Doctor, if you go to Tab 48 of your exhibit,

on page two, this is Detection of Measles Virus Genome Directly From Clinical Samples By Reverse Transcriptive Polymerase Chain Reaction and Genetic Barrier ability.

Under the introduction it's talking about recovering measles virus. Is that true?

A In the abstract or --

Q I'm in the introduction.

SPECIAL MASTER HASTINGS: Page two.

MS. CHIN-CAPLAN: Right.

THE WITNESS: Right.

BY MS. CHIN-CAPLAN:

Q Here did they try to recover measles virus from mononuclear sites on day seven and later after the onset of the rash, and they indicate it's difficult to isolate measles virus from plasma or cerebral spinal fluid using these sensitive methods.

A After the onset of rash. that's different than after the initiation of infection. The rash lasts about five days. That's what I said, once the onset of the rash then you rapidly are much less likely to recover the virus because you've got the immune response.

Q If you know this, that it's difficult to obtain it after seven days, wouldn't it be more likely

that when Atzal and D'Souza did their work that there was not going to be a high likelihood of recovery?

A It depends on if your hypothesis which it seems to be is that there is persistent measles virus replication and persistent measles virus, then you ought to be able to recover it whenever. In other persistent virus infections you can always recover the virus.

So if the hypothesis is that this is persistent measles virus infection, it doesn't matter when. During acute measles virus you get clearance of the virus and then you can no longer recover it.

Q Okay. But even here, it says that it's difficult after the onset of the rash to isolate measles virus from plasma or cerebrospinal fluid.

A Right.

Q The onset of the rash is the onset of the immune response. You rapidly lose your ability to recover, this is infectious virus, to recover infectious virus after that period of time. Those are facts.

Q Okay.

Doctor, you indicated that you were writing a chapter or book with Dr. Oldstone?

A We're just editing a book.

Q And Dr. Oldstone is a very well known virologist, isn't he?

A Yes.

Q He's published a great deal on viral persistence, hasn't he?

A Uh huh.

Q And Doctor, this has been read before, and I'm going to show you Petitioner's Exhibit 61, Tab VV.

(Pause.)

Doctor, if you just read along with me here.

A Where are you reading?

Q In the introduction. Let's start with the second full paragraph. It says that the three foundations upon which the understanding of persistent infection rests are first the host immune response fails to form or fails to purge virus from the infected host. Thus viral persistence is synonymous with invasion of the host immunologic surveillance system.

Would you agree with that?

A That's one mechanism. We talked about that for the immunosuppressed children who are exposed to measles or a measles vaccine can develop, if you don't induce an immune response, if you're unable to induce an immune response, that is certainly one mechanism

for persistence.

Q So you don't disagree with it.

A No.

Q And then it says recent advances have shed light on the cellular molecular players involved. Second, viruses can acquire unique components or strategies of replication. That is viruses can regulate expression of both their own genes and host genes to achieve residence in a nonlytic state within the cells they infect.

You would agree with that, right?

A Right. He's mainly talking about lymphocytic correal meningitis virus there which is what he studies.

Q Right.

Third, the type of diseases that persistent viruses cause are often novel and unexpected. Would you agree with that?

A They can be, sure. You have to know that the virus is there in the organ that's relevant.

Q Okay. And Doctor, if you go further down, the next sentence, the continuous replication of a viral foreign gene in a differentiate cell can selectively disorder the functions of that cell without destroying it.

A He's shown that with LCMV.

Q Okay.

Several examples of viruses that interfere with the ability of neurons to make neural transmitters.

A That's what he did with LCMV.

Q Okay.

A But there was no problem with showing the virus was there.

Q The result is a disturbance in the host biologic equilibrium. Thus one important direct affect of persistent virus replication is to disorder the normal homeostasis of the host and thereby cause disease without destroying the infected cell. Would you agree with that?

A As I say, these are all very virus specific types of things, but you can find examples.

Q The next sentence down, associated disorders and synthesis or release of cytokines, antibodies and other molecules made by immune cells can lead to either immunosuppression on the one hand, or hyperimmune, autoimmune responses on the other. That's --

A In isolated incidences.

Q You don't disagree with any of that.

A No.

Q Okay.

MS. CHIN-CAPLAN: If I can have a minute, Your Honor.

SPECIAL MASTER HASTINGS: All right. For any of you at home who may be signing off before we end here, I'll let you know we will be starting again tomorrow morning at 9:00 a.m..

MS. CHIN-CAPLAN: Special Master, can I just have a five-minute break so I can find this document? It's somewhere in my papers.

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

(Whereupon, a short recess was taken.)

SPECIAL MASTER HASTINGS: All right. We finished our short break here, and we're going to continue with the cross-examination of Dr. Griffin by Ms. Chin-Caplan.

BY MS. CHIN-CAPLAN:

Q Dr. Griffin, can I ask you to just read this editorial?

A The whole editorial?

Q Yes.

SPECIAL MASTER HASTINGS: Wait a minute. Let's mark this first.

THE WITNESS: Come on. It's four pages long.

SPECIAL MASTER HASTINGS: Wait a minute here. Just wait, okay? First we're going to mark this, and it's Petitioner's Trial Exhibit what? Where are we at? No, 16 was Dr. Verstraeten's letter, so I think it's Petitioner's Trial Exhibit 17.

(The document referred to was marked for identification as Petitioner's Trial Exhibit No. 17 and was received in evidence.)

SPECIAL MASTER HASTINGS: And, Ms. Chin-Caplan, as Dr. Griffin just said, this is three pages, very, very long pages, lots on the page. You don't seriously want her to read the whole thing into the record? I mean, we're going to file this, so it's going to be in the record.

MS. CHIN-CAPLAN: Okay.

SPECIAL MASTER HASTINGS: It's in the record as soon as it's filed.

MS. CHIN-CAPLAN: I shall target everything.

SPECIAL MASTER HASTINGS: Okay.

MS. CHIN-CAPLAN: I'm really looking at the section that begins on page 122. It talks about

constellation features which make up the MINE syndrome.

SPECIAL MASTER HASTINGS: All right. I see that. Do you see that on page 122?

THE WITNESS: Unfortunately, MINE syndrome isn't something that I've heard of.

SPECIAL MASTER HASTINGS: I'm sorry. I didn't hear what you said, Doctor.

THE WITNESS: I just said the MINE syndrome is something I've never heard of.

SPECIAL MASTER HASTINGS: All right.

THE WITNESS: So I'll get educated.

(Pause.)

THE WITNESS: So can you tell me where this was actually? They're quoting all these virus isolations.

BY MS. CHIN-CAPLAN:

Q Are you through reading, Doctor?

A What?

SPECIAL MASTER HASTINGS: What did you --

THE WITNESS: I don't know what you're trying to --

SPECIAL MASTER HASTINGS: What did you want her to read? The whole?

MS. CHIN-CAPLAN: I guess I can stop, and if

you need to read, then you let me know, okay?

SPECIAL MASTER HASTINGS: Okay. That sounds like a good idea.

MS. CHIN-CAPLAN: Okay.

BY MS. CHIN-CAPLAN:

Q Now, Doctor, do you recognize Dr. Paul Dyken?

A No.

Q Do you know that he is a pediatric neurologist?

A No.

Q Do you know that he maintains the SSPE registry for the United States?

A No.

Q So, Doctor, in this article, is he comparing SSPE to what he calls measles-induced neuroautistic encephalopathy?

A I guess so.

Q Okay. And the acronym is MINE, M-I-N-E, correct?

A I guess so. As I say, it's something I'm unfamiliar with.

Q Okay.

A Not mainstream, put it that way.

Q Yes. And, Doctor, he's essentially

describing the autistic enterocolitis population, isn't he?

A Well, it looks like it. As I say, I haven't had a chance to read it in depth, but glancing at it, it looks like what he's doing.

Q Uh-huh. And if you go to page 123, on the first full paragraph, he says, "An opinion can be given that MINE develops in the same fashion as does SSPE. Although the syndromes are different, the etiology and the pathogenesis are similar. For both syndromes, two factors are required: an immature or defective immune system which is unable to inactivate the attacking measles virus, whether it is the wild or the live attenuated form.

"In the situation of SSPE, the full antigenic wild virus is only partially inactivated, allowing the remaining aborted form to escape and harbor within the large neurons of the cerebral cortex where they are sheltered and persist to grow."

And we know that happens in SSPE, correct?

A Correct.

Q And then if you go to the next column, nine lines down, he states, "Those who develop MINE do not completely neutralize the live attenuated virus and an aborted form of the virus ensues."

A Okay. What I'm trying to figure out is where the proof is that the virus is in the brain.

Q This is what he's saying, isn't that true, reading what his statement is?

A No, no, no. But "An opinion can be given." This is his opinion.

Q And that's what I'm saying, Doctor. I am reading what he has written, is that true?

A Right. But I'm just saying it's his opinion. He doesn't have data.

Q Okay.

A I'm big on data.

Q "The aborted form escapes and harbors in the nervous system in particularly susceptible areas such as the hippocampus, limbic system and older portions of the cerebral cortex where the blood-brain barrier is less protective." Have I read that correctly?

A You actually read quite well.

Q Thank you. Okay. And then further down, Doctor, approximately a third of the way down, there's a sentence that begins, "Opposed to the lengthy period of quiescence seen in SSPE, when the escape of the aborted, partially damaged wild measles virus acts upon the larger neurons residing in neocortical areas, the interval period in MINE is only a matter of

months.

"It would appear that breakout is not as devastating as in SSPE, and the clinical symptoms after the short interval may be more due to chronic sapping of the selected host cell's metabolic activity." I read that correctly?

A You did.

Q Yes. Now, Doctor, in Michelle Cedillo's case, measles RNA was recovered in her gut, wasn't it?

A Measles was reported to have been found by RT-PCR in her gut.

Q Yes.

A But as I think I emphasized, I think it's a result that is highly suspect.

Q Okay.

A And it's the only thing that links it to measles.

Q Yes.

A Her whole case.

Q Yes.

A Okay. So a lot hangs on it.

Q And, Doctor, do you know that Michelle has bowel symptoms?

A Yes.

Q And do you know that she has recently

started treatment with Humira for inflammatory bowel disease?

A Yes. It's sort of amazing that you'll immunosuppress somebody you think has a persistent virus infection.

Q But, Doctor, you do know that?

A Yes.

Q Yes. So, in your opinion, and you can certainly tell me whether you have an opinion or not, do you believe that the positive measles finding in the gut is related to her inflammatory bowel disease?

A No. I don't think it's a positive measles finding in the gut. I mean, I don't believe that result, put it that way.

Q Okay.

A So, therefore, I don't think there's a link.

Q Well, Doctor, if I asked you to assume that fact, that is, that real finding, that it's true --

A Okay. All right.

Q -- would you assume then that her inflammatory bowel symptoms are related to the measles?

A No, because on the biopsy, there was no evidence of inflammation of measles virus pathologic changes, I mean, nothing that would suggest that would

give her all these symptoms.

Q Well, let me ask you this question, Doctor. If you assume that there is positive measles virus recovered in CSF, blood and gut, would you believe that --

A Has there been positive virus recovered?

SPECIAL MASTER HASTINGS: Let her ask. It's a hypothetical.

THE WITNESS: Okay.

BY MS. CHIN-CAPLAN:

Q Would you assume that if a child had a neurological condition that it was related to the positive measles virus that was found in the CSF?

A Well, I think if you found measles in the CSF of this child, that would be a very significant finding, and you'd want to make sure that was true. You would expect to see a lot of other things related to a persistent virus infection of the nervous system like changes on EEGs, scanning of various varieties and increased production of antibody in the CSF, which you would have done on the same sample I assume.

But absolutely, if you're finding it in the nervous system, then that would be an important observation, and it should definitely be followed up and figured out.

MS. CHIN-CAPLAN: Okay. Thank you. I have no further questions, Special Master.

SPECIAL MASTER HASTINGS: All right. Any questions?

(No response.)

SPECIAL MASTER HASTINGS: Ms. Chin-Caplan, you put up on the board an excerpt from Exhibit R, Tab 18.

MS. CHIN-CAPLAN: Exhibit R. I'm sorry.

SPECIAL MASTER HASTINGS: Tab 18. You asked some questions about trenchant symptoms. Mr. Shoemaker, you know what I'm talking about?

MR. SHOEMAKER: I'll try to get to it, sir.

SPECIAL MASTER HASTINGS: Okay.

MS. CHIN-CAPLAN: Oh, that's the chapter in *Fields Virology* by Dr. Griffin.

SPECIAL MASTER HASTINGS: Yes. Yes, it was. Okay. Can you put that back up?

(Pause.)

SPECIAL MASTER HASTINGS: The page number that you had? I never heard a page number.

MR. SHOEMAKER: Fourteen twenty-seven.

SPECIAL MASTER HASTINGS: Oh, it was 27.

MS. CHIN-CAPLAN: Fourteen.

SPECIAL MASTER HASTINGS: Yes. Fourteen

twenty-seven. All right. That's what I heard, but I thought someone said that that was -- but that is the correct page. Can you highlight the part that you had highlighted before just as a lead here for me?

All right. So do you have that in front of you, Doctor? It's the lower right-hand corner of the page.

THE WITNESS: Uh-huh.

SPECIAL MASTER HASTINGS: You were asked about this sentence, beginning of the paragraph, "Administration of standard doses of live attenuated MV-C results in trenchant lymphopenia." You were asked about that.

THE WITNESS: Right.

SPECIAL MASTER HASTINGS: The second clause there, "Suppression of delayed hypersensitivity skin test responses to recall antigens." Now, in the first one, you said trenchant lymphopenia.

THE WITNESS: Uh-huh.

SPECIAL MASTER HASTINGS: Lymphopenia I should say.

THE WITNESS: Right.

SPECIAL MASTER HASTINGS: In this one, you don't use the word trenchant, but is this a trenchant effect?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: The next clause, "Decreases in antigen and mitogen-stimulated proliferation of lymphocytes." Is that also trenchant?

THE WITNESS: Yes.

SPECIAL MASTER HASTINGS: And then the fourth clause, "Altered cytokine production." Was that also trenchant?

THE WITNESS: Yes. Yes.

SPECIAL MASTER HASTINGS: All right. All right. I don't have anything further for this witness. Did you have any redirect?

MR. MATANOSKI: I did, sir. However, having been handed this editorial that it seems like it would have been in the case-in-chief, perhaps attached to Dr. Kinsbourne's report since it talks about some postulate of SSPE or measles persistence that's associated with autism, I'd like to actually have Dr. -- I hate to do this.

I'd like to have Dr. Griffin take a closer look at it as I just have and before I ask her questions offer any opinions she might have on this after taking a further review. So I hate to do it, sir, but I'd ask for just a few minutes to let her

take a quick look at this.

SPECIAL MASTER HASTINGS: Well, I was kind of stunned to see this editorial. This seems to be new evidence offering at least some support to your theory of the case. It's a three-year-old editorial, and it comes in at 7:00 on the last day of trial. It seems surprising to say the least. So, in those circumstances, what kind of a break are you talking about?

MR. MATANOSKI: I'd just like about five minutes so that Dr. Griffin can take a look at it.

SPECIAL MASTER HASTINGS: All right. Let's take a five-minute break. And if you decide you want to file something, a written report later on to respond to this --

THE WITNESS: I was going to say maybe we could do that. I'd be glad to write something.

SPECIAL MASTER HASTINGS: Please, Doctor, one of us can only talk at a time or the reporter can't get it down. If you decide you'd rather have a written response to this at a later date, that would be acceptable too.

MR. MATANOSKI: Actually, sir, that probably would be the better way to do that so that Dr. Griffin doesn't have to be put on the spot here to read

quickly and digest this all at once.

And in fact, sir, that may make it unnecessary for the second part of what I was going to talk about with respect to this particular document, which is that this may require rebuttal testimony by other witnesses that I had released at this point based on the notion that there would not be rebuttal by Petitioners' witnesses in those areas since this touches also on areas beyond measles virology it would seem.

But if we were to permit us to take a look at this or if you were to permit us to take a look at it, have our experts review it and if necessary reply by written report, I think that would take care of that as well, sir.

SPECIAL MASTER HASTINGS: All right. Well, we'll permit such a thing because of the time at when this document is coming in.

MR. MATANOSKI: Thank you, sir. Then I only have a few questions.

SPECIAL MASTER HASTINGS: Okay. Go ahead.

REDIRECT EXAMINATION

BY MR. MATANOSKI:

Q I think the last article you were looking at in response to the Special Master's questions, he went

through that these were all trenchant changes. There was also a further sentence in that paragraph that you were looking at in *Fields Virology*. I believe that sentence went to whether or not you believed these changes were clinically relevant.

A I don't have it up in front of me.

Q I know. I know you don't.

A But I do not think that these changes are clinically relevant.

Q I just want you to affirm or not whether you believe those changes are --

A I do not think they're clinically relevant.

Q With respect to there was some discussion about memory response, do you think they're clinically relevant changes after the induction of measles vaccine in this memory response?

A No.

Q Is anything in your opinion with regard to the PCR based on access that you've had to materials through the MMR litigation in the United Kingdom?

A Not that I know of.

Q You didn't use any of that material in writing your report?

A I did not.

Q You mentioned that Dr. Wakefield asked you

to come over to look at his --

A Yes. That was very early. I think it was probably 1998. He had a meeting that he used to have at Wellcome Trust, which was funding him early on, and he would invite somebody to be speaker basically or an outside person, and so I was invited one year and I was aware of the controversy. And as I say, it was early on when he was just beginning to implicate MMR as a cause of autism, and so I was curious, so I went.

I spoke, I interacted with the people in the lab. They were having a lot of trouble trying to make their PCR work. They couldn't reproduce the immunocytic chemistry that they had one slide of in the gut. I mean, they presented those data at that conference. It was an open scientific meeting. So I had a little bit. I had nothing else to do with it after that, but I had a little bit of insight, a little bit of knowledge about sort of the lab and the thinking and that sort of thing.

Q Were they recovering measles virus?

A No. No, I mean, if you really want to know, I mean, frankly, they did not have a hypothesis of what the connection -- at that time, they did not have a hypothesis of the connection between MMR and measles and autism and were sort of looking for something that

would link them.

Q With respect to the Uhlmann study, you were asked some questions and you looked through your report. I understand you to say that sequencing was a problem from what you could see in publicly available information and other factors, only publicly available information. Did you see other --

A Right. Well, the blinding of the samples is really a critical thing because if people know which ones are the patients and which ones are the controls, and there was no evidence in that paper that those samples were blinded or coded or something, I mean, all of us have to do that because we're prejudiced. We're looking for something. We have a hypothesis. We would like for it to be proved. So it's just a very critical part of data collection.

Q You were presented with a series of statements from Dr. Oldstone in something that he had published I think recently. Now you're working with Dr. Oldstone in publishing some work on virology, is that right?

A Right. Well, yes. We're colleagues. I mean, we're in the same field basically. I've known him for a long time.

Q Okay. That series of statements that you

were asked if you agreed whether or not they were written there, could you comment on that series of statements with respect to measles virus?

A Well, those are all very generalized statements about the whole world of virology, so I don't know how many different hundreds of viruses can cause of infections of all different varieties. And you can certainly find examples of them that would do each of these things. He has mainly studied a mouse virus, which is lymphocytic choriomeningitis virus where he infects the animals at a very early age and then he can see developmental abnormalities with that particular mouse virus.

And so I don't disagree with that, but none of them have been observed. I mean, it's not very relevant or very specific. It certainly isn't specific for measles, and so these are very general statements that are true for one virus or another, but you can't conclude that all of them could be true for measles.

Q As far as wild measles virus is concerned, is there any reason to conclude that gastrointestinal symptoms that are observed were caused by the wild measles virus?

A The gastrointestinal?

Q Were caused by the virus itself, the wild measles virus itself?

A Right. There hasn't been evidence of that because diarrhea itself is not usually a component of measles without the secondary infection.

Q How about the same question, but this time it's a vaccine virus?

A Oh, I don't know that there's any evidence that diarrhea is -- I mean, the wild type virus, diarrhea is associated with the disease, but that's not true with vaccination.

Q How long have you studied measles virus?

A Probably about 30 years.

Q Okay. In your study of measles virus over that period of time, I understand you've studied it in population, right, and in the lab. You've also studied vaccine virus. Any reason in your mind after 30 years of study to conclude that persistent measles virus would result in autism?

A No.

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

SPECIAL MASTER HASTINGS: Anything further for this witness, Ms. Chin-Caplan?

MS. CHIN-CAPLAN: Two questions.

SPECIAL MASTER HASTINGS: Okay.

RECROSS EXAMINATION

BY MS. CHIN-CAPLAN:

Q Doctor, you indicated that there was a problem with blinding in the Uhlmann study. Where is that located in his article?

A Well, what you look for is that they say they did it. I mean, anybody that does it makes sure people know that.

Q Wouldn't you assume that they would act in accordance with the standards of their profession?

A All I have to say is there are a lot of publications out there from people who don't blind samples, and it's a problem. And so I can't assume that. I cannot assume that. All I can say is if people blind samples, they make sure that it's stated in the methods.

Q Do you know the reputation of the O'Leary lab at all?

A Oh, yes.

Q And what is the reputation?

A It's not very good.

Q That's what you're saying? It's not very good?

A Right. The reputation. You're asking about

the general reputation in the scientific community?

Q Yes.

A Absolutely. Yes.

Q And, Doctor, you indicated that you went to see Dr. Wakefield in was it 1998?

A Well, no, I wouldn't want to be held to the date, but it was very early in this, putting forward this hypothesis that MMR caused -- and at that time, it was specifically MMR, the measles component of MMR, which I guess is the persistent hypothesis.

Q And at that time, Doctor, were you a member of the Scientific Affairs Committee for Merck?

A I was a member of their Scientific Advisory Board at Merck for a period of three or four years, and I have no idea whether that overlapped or not. I'd have to go back to my calendar to figure that out.

Q Okay. And Merck makes the MMR, doesn't it?

A In the U.S., but in the U.K., there's three vaccine manufacturers.

MS. CHIN-CAPLAN: Okay. Thank you.

SPECIAL MASTER HASTINGS: Anything further for this witness?

MR. MATANOSKI: Just one followup.

FURTHER REDIRECT EXAMINATION

BY MR. MATANOSKI:

Q With respect to that last question, was your opinion of the work done by Dr. Wakefield influenced in any way by being on the Science Advisory Board or being somehow Science Advisory personnel for Merck?

A No. No, not at all. That's irrelevant.

MR. MATANOSKI: That's it, sir.

(Witness excused.)

SPECIAL MASTER HASTINGS: All right. I think we're done for the day. Let me ask Ms. Chin-Caplan, now tomorrow morning you're planning to present some more testimony from Mrs. Cedillo, is that correct?

MS. CHIN-CAPLAN: That's correct, Special Master.

SPECIAL MASTER HASTINGS: Anything else?

MS. CHIN-CAPLAN: Aside from closing, no, that's it.

SPECIAL MASTER HASTINGS: And then the closing argument. All right. So we're done for the day here. We'll start again at 9:00 a.m. tomorrow. We're adjourned.

MR. MATANOSKI: Thank you.

(Whereupon, at 7:15 p.m., the hearing in the above-entitled matter was adjourned, to reconvene on Tuesday, June 26, 2007, at 9:00 a.m.)

REPORTER'S CERTIFICATE

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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 Office of Special Masters.

Date: June 25, 2007

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