

IN THE 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.)

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	--	--

2499

E X H I B I T S

PETITIONER'S EXHIBITS:	IDENTIFIED	RECEIVED	DESCRIPTION
15	2639	2639	Newschaffer study
16	2699	2699	Slide
17	2848	2848	Editorial
RESPONDENT'S EXHIBITS:			
21	2654	2654	Slide
22	2640	2640	Letter to the Editor

2500

1 PROCEEDINGS

2 (9:02 a.m.)

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

5 Mr. Matanoski, who will be your first
6 witness?

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

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

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

13 Whereupon,

14 ERIC FOMBONNE

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

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

20 MS. RICCIARDELLA: Thank you.

21 FURTHER REDIRECT EXAMINATION

22 BY MS. RICCIARDELLA:

23 Q Welcome back, Dr. Fombonne. Good morning.

24 A Good morning.

25 Q You're an epidemiologist, correct?

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FOMBONNE - FURTHER REDIRECT

1 A Yes.

2 Q What is epidemiology?

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

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

10 A Yes.

11 Q What are the different epidemiologic study
12 designs?

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

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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FOMBONNE - FURTHER REDIRECT

1 characteristic that you want to relate to the disease.

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

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

7 A Yes.

8 Q What is that?

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

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

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FOMBONNE - FURTHER REDIRECT

1 The reason is in these ecological studies we
2 only have access to aggregated data, and we never know
3 at the individual level who was exposed and who was
4 actually diseased, so there could be some spurious
5 correlations which arise from these ecological
6 studies.

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

9 THE WITNESS: Yes?

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

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

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

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

20 BY MS. RICCIARDELLA:

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

24 A Yes. When we conduct studies we measure
25 disease occurrence in populations in different

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FOMBONNE - FURTHER REDIRECT

1 measures of

2505A

FOMBONNE - FURTHER REDIRECT

1 disease occurrence.

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

10 Attached to this proportion you can
11 calculate a confidence interval to provide some
12 measure of a certainty about the true parameter and
13 the population.

14 Q What are incidence?

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

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

25 So you follow them up, for instance, five

2506A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

2508A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

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

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FOMBONNE - FURTHER REDIRECT

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

6 It started with a CDC study in New Jersey,
7 which was published in 2001. There was another major
8 effort in Atlanta published in 2003. Then the CDC
9 actually, concerned with rates of autism and the fact
10 that there were no U.S. data on that, started in early
11 2000 I think to develop a monitoring program for
12 autism epidemiology in the U.S., and just this year in
13 February they released the first results of two major
14 surveys of autism spectrum conditions in the U.S.

15 What they did was to look at children who
16 were eight years old, and they looked at them in
17 various states in the U.S. In one study there are 14
18 states involved in this monitoring project all
19 concentrating on eight-year-olds.

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

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

2510

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

2511A

FOMBONNE - FURTHER REDIRECT

1 New Jersey in eight-year-olds in 2002 the rate was
2 1.07 percent of the population had an autism spectrum
3 disorder, 1.07 percent. That's the highest rate that
4 we see.

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

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

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

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

25 Q So, Doctor, you would agree that prevalence

FOMBONNE - FURTHER REDIRECT

1 rates for autism are higher than in years past?

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

6 I know at least of about 12 published
7 studies which show rates which are consistently around
8 60 to 70 per 10,000, which is probably the best
9 estimate that we have today. These studies have been
10 done by different groups of investigators using
11 different methods. They come from the U.K. They come
12 from Canada, from the U.S -- there are multiple
13 studies now -- and also from Scandinavia, the Faroe
14 Islands. You name it, there are multiple replications
15 of these findings in recent studies.

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

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

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FOMBONNE - FURTHER REDIRECT

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

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

10 Q Does the change in diagnostic criteria
11 affect prevalence rates?

12 A Yes. Absolutely. This is now Slide 6. It
13 portrays in the slide the evolution of nosographies,
14 and DSM-II in 1968 there were basically no provisions
15 made for child psychiatric disorders.

16 The first really criteria for autism were
17 developed by Michael Rutter in England in 1970. They
18 were subsequently embodied in 1979, in 1975, and then
19 in the U.S. it's really started to change in 1980. In
20 1980 that there was the first time that the notion of
21 PDD was coined in the literature.

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

2514A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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FOMBONNE - FURTHER REDIRECT

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

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FOMBONNE - FURTHER REDIRECT

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

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

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

10 They did one study, one survey. They
11 collected their data, and therefore the data do not
12 change, they are there. What they did, they applied
13 to this same data set different diagnostic criteria to
14 see how changing the diagnostic criteria affects the
15 results.

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

22 So you have here a demonstration that
23 diagnostic criteria can account for a threefold
24 difference or increase in the rates themselves. Of
25 course, it might not be as often the case in other

2515B

FOMBONNE - FURTHER REDIRECT

1 studies, but that's a very clear demonstration that

2516A

FOMBONNE - FURTHER REDIRECT

1 diagnostic criteria can impact substantially the
2 prevalence estimates in studies.

3 Q Does case ascertainment affect the
4 prevalence rates of ASD?

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

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

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

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

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1 and

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1 that in turn can affect the findings and the yield of
2 cases in our studies.

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

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

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

24 This is a kind of passive way to identify
25 case studies that are known in other domains of

2517B

FOMBONNE - FURTHER REDIRECT

1 epidemiology.

2518A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

2519A

FOMBONNE - FURTHER REDIRECT

1 due to design features of studies which are not
2 comparable.

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

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

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

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

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

2520A

FOMBONNE - FURTHER REDIRECT

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

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

17 What's happening from left to right is that
18 there is a transfer from the population pool of cases
19 towards those who are accessing services, and if you
20 only concentrate on the number of dots in the pink
21 area you will generate a trend which up, a very, very
22 low access and a high number later. You have an
23 upward trend.

24 In fact, we must, to evaluate the trend,
25 have access to the population estimates. Unless you

2521A

FOMBONNE - FURTHER REDIRECT

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

4 These are all what I would call referral
5 statistics, and that involves Department of Education
6 data or health services data, and they are not
7 appropriate to evaluate the trend.

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

10 A Well, this is one illustration from that
11 slide. This is Slide 10. It comes from a paper by
12 Gurney, et al., and it's consolidating municipal data,
13 but the trend that you see is a trend you see in all
14 states or most states in the U.S. and also a trend
15 that you see in England, in Denmark, in Canada, in
16 every country where you have seen trends over time.
17 You have this same type of curve.

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

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

2523A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

16 A Yes. In this study by Shattuck published in
17 2005 is an elegant demonstration that you can have
18 what is called diagnostic switching or diagnostic
19 substitution, and that can explain to a large extent
20 the increases in numbers of children who have
21 currently a diagnosis of ASD.

22 The arrows are a bit off, so I'm going to
23 explain that. On this slide you have the dotted line,
24 which is horizontal on the top, is what you would
25 predict would be the prevalence based on recent

2524A

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

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

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

19 If one looks at this trend over time what is
20 important is in 1994 on the left-hand side, and the
21 arrow is actually not at the right page, but the
22 starting point is an average prevalence of six per
23 10,000, meaning that in 1994 if we just look at the
24 Department of Education data in the U.S. across all
25 states you would estimate that there is about six

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

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

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

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

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

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

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

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

25 SPECIAL MASTER HASTINGS: Let me just add

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2527A

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1 that you're on Slide 12 now, correct?

2 THE WITNESS: Sorry. Yes.

3 SPECIAL MASTER HASTINGS: Go ahead.

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

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

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

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FOMBONNE - FURTHER REDIRECT

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

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

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

22 He quantified this trend, and it was about
23 12 per 1,000 for the increase. If I could go back?
24 And then he looked at the decrease for mental
25 retardation combined with learning disability and

2529A

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

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

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

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

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

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

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

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

13 BY MS. RICCIARDELLA:

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

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

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

22 A Yes. Oh, yes.

23 Q You referred to Slide 14?

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

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1 things.

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

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

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

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

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

3 A Yes.

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

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

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

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

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1 registers, so they identified cases like that.

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

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

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

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

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

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

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

25 They didn't find any difference. There was

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

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

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

18 There was one exception with the parental
19 concern which was that, as you see on that slide,
20 there was parental concern in the sixth month which
21 followed MMR immunization. The rate of incidence is
22 1.48 and is significant, but when they looked actually
23 at the data in the U.K. children receive their MMR at
24 13 months of age, and in that particular data set a
25 lot of parents become concerned at age 18 months.

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

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

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

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

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

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

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

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

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

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1 birth registries over Georgia.

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

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

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

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

23 A Yes. That's on Slide 18. Now, this was a
24 very important study because of its location, which is
25 Denmark, and the huge statistical power.

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

8 The design is very simple. It's to look at
9 children who were born between 1991 and 1998, and that
10 covers in that study half a million children in that
11 study, so it's really powerful. Then you follow
12 children between the age of one up to the point where
13 there is either death or the end of the followup
14 period or a diagnosis of autism so you can really --
15 it's like a cohort study.

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

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

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

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

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

22 What was the objective of your study?

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

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

5 In the U.K. there is what is called a GPRD,
6 which is a General Practice Research Database, which
7 contains -- it varies, but sometimes contains up to
8 400 or 500 general practices across the country, and
9 it covers several million people who were attending
10 these GPs.

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

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

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

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

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

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

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

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

22 We restricted our analysis to children born
23 before that, and therefore the parental behavior or
24 the GP behavior would not be affected by that. Again,
25 that is the reason we had do so there is a range of

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1 different

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

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

7 MS. RICCIARDELLA: Slide 21.

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

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

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

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

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

11 The actual value of this pool estimate is
12 0.87. It's not significantly different from one, but
13 again it's the value which is attached to the
14 association between MMR, again which shows in effect
15 no association across four the different study.

16 BY MS. RICCIARDELLA:

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

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

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1 reflected in increased consultations with that child's
2 doctor.

3 What were the conclusions though of this
4 DeWilde study?

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

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

19 That's what they did. They looked in
20 another electronic database called the Doctors
21 Independent Network, and they had children who
22 ultimately were diagnosed with autism, 71. They
23 matched them to four controls per case, so 284
24 controls.

25 They had the MMR immunization dates, and

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1 they

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

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

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

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

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

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

10 I'd like to refer to a study that you did in
11 2004 that was published in the Journal of
12 Psychological Medicine, and I'm referring to -- I
13 don't have that page.

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

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

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

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

4 If we can have the next slide?

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

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

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

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

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

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

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

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

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

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

7 MS. RICCIARDELLA: Technical difficulties.

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

10 BY MS. RICCIARDELLA:

11 Q All right. Moving on, your findings have
12 been shown in other studies as well, for instance, a
13 study by Dales, et al. that was published in JAMA in
14 2001. I'm referring to Exhibit P at Tab 33.

15 A Yes. This is another ecological study which
16 was done in the U.S. The data actually originates
17 from California. It does encompass young children
18 diagnosed with autism in the developmental centers of
19 California, and you see the trend is from 1980 to
20 1994.

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

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

3 This estimate is obtained regularly by
4 surveys which are conducted in kindergarten schools,
5 both private and public, across the state of
6 California. The usual sample size that they use is
7 600 to 2,000, so it provides an estimate for coverage
8 and a trend that you can use.

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

18 So this is Slide 28.

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

22 What did this study consider?

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

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

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

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

18 A Yes.

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

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

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

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

12 So what we found, and this is the next
13 slide, is this is first portraying the rate of autism
14 in each successive birth cohort. You can see the
15 children who are born between 1987 on the left up to
16 1998 on the right. The survey was done in 2003, so
17 children were age five to 17.

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

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

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

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

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1 understand.

2 In Quebec there was one MMR dosing schedule
3 up to 1995 and then they decided to increase the
4 vaccination coverage and to introduce from 1996 onward
5 a second MMR dose, so the first MMR dose was given at
6 12 months of age, and the second MMR dose, which was
7 given after 1996, is given at 18 months of age.

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

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

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

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

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

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

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

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

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

4 It was soon recognized as a problem, and as
5 a result of that they actually advised to discontinue
6 the use of MMR in Japanese children, and then they
7 reverted it in 1992 to the use of monovalent measles
8 vaccine. So what we see here is from 1988 through
9 1992 you see the decline in the use of the MMR vaccine
10 in Japan, and then in 1992 it stops altogether.

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

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

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

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

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

7 A Yes.

8 Q What did you tell them?

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

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

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

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

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1 different

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1 clinical correlates.

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

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

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

25 I reviewed very carefully Dr. Wakefield's

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1 paper and his own presentation at the MRC in 1998. In

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

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

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

24 BY MS. RICCIARDELLA:

25 Q Doctor, if MMR were causally linked to the

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

4 A Yes.

5 Q Is that the case?

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

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

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

18 THE WITNESS: Yes, 35. I could provide
19 quotes by multiple British scholars or even Kanner in
20 1943 described regression in some of his relevant
21 cases.

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

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

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

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

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

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

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

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

7 BY MS. RICCIARDELLA:

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

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

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

17 A Yes.

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

20 What did this study investigate with regard
21 to regression?

22 A This is Slide 37.

23 Q Very good.

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

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

5 Again, the key point here is that 1988 is
6 the MMR introduction in the U.K., so the first
7 analysis is to look at trends over time in regression.
8 When they looked at that using methods which were
9 multivaried analysis adjusting for various factors
10 there was absolutely no evidence that there was an
11 increase in the proportion of children who were having
12 regressive autism over this period which spans 1979 to
13 1998.

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

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

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

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

13 A This is Slide 38, and again, they relied on
14 sort of a quasi-experiment, which is that there was a
15 phase where there was no MMR, then there was
16 introduction of MMR, and then there was this
17 confusion, then there was a -- it was a nice design,
18 because you can see, if there were, you should see the
19 rates of regression which fluctuates according to
20 which period you are investigating, and then the way
21 it's presented is a bit special in their paper.

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

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

FOMBONNE - FURTHER REDIRECT

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

8 So that's what we tested immediately in
9 1998, because we had data which could allow us to do
10 that, and in short, there is an English Maudsley
11 Hospital series of children with PDDs, 762,
12 psychiatric controls, 100 -- 8,000 or more, and then
13 there is a French series of epidemiological data, 174
14 children with PDDs and almost 6,000 psychiatric and
15 developmentally impaired controls.

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

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

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

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

8 THE WITNESS: Yes.

9 BY MS. RICCIARDELLA:

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

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

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

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

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

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

25 Q Doctor, before you talk about the study you

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1 published in 2001, I just wanted to make sure that the

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

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

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

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

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

FOMBONNE - FURTHER REDIRECT

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

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

12 A Yes.

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

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

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

FOMBONNE - FURTHER REDIRECT

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

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

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

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

25 So children are followed from birth to age

FOMBONNE - FURTHER REDIRECT

1 14 months, and as they age, in an increasing number
2 receive the vaccination, and this is called a survival
3 curve.

4 SPECIAL MASTER HASTINGS: What kind of
5 curve?

6 THE WITNESS: Survival.

7 SPECIAL MASTER HASTINGS: Survival?

8 THE WITNESS: Survival curve.

9 SPECIAL MASTER HASTINGS: Survival of the
10 fittest.

11 THE WITNESS: Yes, okay.

12 SPECIAL MASTER HASTINGS: Okay.

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

FOMBONNE - FURTHER REDIRECT

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

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

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

FOMBONNE - FURTHER REDIRECT

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

7 BY MS. RICCIARDELLA:

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

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

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FOMBONNE - FURTHER REDIRECT

1 striking.

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

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

16 Q I'd like to shift focus now. We were
17 talking about epidemiologic studies that looked at the
18 MMR autism hypothesis. Now I'd like to briefly
19 discuss some of the studies that have been done that
20 have looked at the possible causal association between
21 thimerosal-containing vaccines and the development of
22 autism. And we won't go through them all, but I would
23 like to first ask you about a study done in Denmark by
24 Hviid et al., published in JAMA in 2003, and I'm
25 //

FOMBONNE - FURTHER REDIRECT

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

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

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

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

2579A

FOMBONNE - FURTHER REDIRECT

1 group who received at least some thimerosal-containing
2 vaccines.

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

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

22 Again, the study is actually well powered,
23 the national representative sample, no effect.

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

FOMBONNE - FURTHER REDIRECT

1 2003, and I'm referring to Respondent's Exhibit P at
2 tab 106. What did this study look at specifically?

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

13 And what is clear from this graph is that
14 the rates of autism are flat from 1970 to about 1989
15 or 1988, and then they start to increase, before,
16 actually, the thimerosal is discontinued. Thimerosal
17 doesn't change, there is no increase or no change in
18 the thimerosal content of vaccines between 1988 and
19 1992, but the rates start to increase. And then what
20 is more even striking is that when thimerosal is
21 removed in 1992, there is no evidence that the rates
22 are falling down or changing in their slope.

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

2581A

FOMBONNE - FURTHER REDIRECT

1 population.

2 Q Now Doctor, you did a study that we've
3 already discussed, the Montreal, Quebec study, and you
4 looked at children born in Montreal between 1987 and
5 1998, and you also, with respect to thimerosal-
6 containing vaccines, what did your study consider?

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

16 And there is a two source period when we've
17 looked at the cumulative column on the right, a period
18 where the total amount of ethyl mercury in that case
19 is about 100 or 125 micrograms based on the official
20 immunization schedule, which is outlined on the slide.
21 And then in 1992, there is a change because more dose
22 of HiB are introduced, and that led to several years,
23 four years as I recall, where the vaccines contained
24 up to 200 micrograms.

25 And then in 1996, the Quebec authorities

2582A

FOMBONNE - FURTHER REDIRECT

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

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

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

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

FOMBONNE - FURTHER REDIRECT

1 where the exposure is nil.

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

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

22 BY MS. RICCIARDELLA:

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

FOMBONNE - FURTHER REDIRECT

1 A Yes.

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

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

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

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

FOMBONNE - FURTHER REDIRECT

1 concluded?

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

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

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

FOMBONNE - CROSS

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

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

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

13 (Whereupon, a short recess was taken.)

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

19 MR. POWERS: Thank you, Special Masters.

20 CROSS-EXAMINATION

21 BY MR. POWERS:

22 Q Good morning, Dr. Fombonne.

23 A Good morning.

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

FOMBONNE - CROSS

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

7 A I think so, yes.

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

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

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

FOMBONNE - CROSS

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

3 A Yes, correct.

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

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

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

20 A Yes, that's correct.

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

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FOMBONNE - CROSS

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

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

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

12 A No. No, no, the --

13 Q How many more are there?

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

22 And in the DSM-IV diagnostic system, in
23 fact, you have the diagnostic criteria, there are only
24 12 diagnostic criteria in DSM-IV, and these are more
25 there for symptom groupings if you wish.

FOMBONNE - CROSS

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

4 A Yes.

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

13 A Yes, it's fair.

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

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

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

FOMBONNE - CROSS

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

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

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

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

22 A Yes.

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

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FOMBONNE - CROSS

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

3 A The methodology of?

4 Q Of diagnosis.

5 A It's one of the factors.

6 Q And others might be case ascertainment?

7 A Yes.

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

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

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

FOMBONNE - CROSS

1 causation, if I recall, you discussed, and I'm not
2 going to get into detail on this, but just to really
3 try to focus us again on what the epidemiology is
4 looking at, you talk about the genetics. And if I
5 recall, at some point in your testimony, you indicated
6 that as many as 20 different genes might be implicated
7 in the etiology of autism. Is that approximation of
8 20, is that a fair re-statement of what your opinion
9 would be?

10 A I don't recall having said exactly that.

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

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

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

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FOMBONNE - CROSS

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

4 Q I'm sorry, most parsimonious?

5 A Yes, the most parsimonious model. Our data
6 were consistent with anywhere between three to up to
7 15 or 20 genes. Neil Rich in the U.S. has done other
8 kinds of modeling techniques. He has quoted like more
9 15 or 20 genes. So I don't know, but yes, a fair
10 number of genes.

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

19 A Yes.

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

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

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FOMBONNE - CROSS

1 fashion. That's right. Yes. At the moment we assume
2 that genes contribute a lot to the population variance
3 of this condition, but we assume that there is genetic
4 heterogeneity, meaning that genes will be different in
5 different families or complete sets of genes will be
6 different in different families.

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

10 A Yes.

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

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

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

FOMBONNE - CROSS

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

9 A Depends what you mean by that.

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

13 A Yes.

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

19 A Yes.

20 Q And one of those criteria is specificity,
21 correct?

22 A Yes.

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

FOMBONNE - CROSS

1 atypical autism. Do you recall that description?

2 A Yes.

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

6 A Correct.

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

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

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

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

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

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

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

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

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

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

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

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

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

25 MR. MATANOSKI: I think Mr. Powers' question

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

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

5 THE WITNESS: Sorry. Can you repeat the
6 question?

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

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

20 BY MR. POWERS:

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

FOMBONNE - CROSS

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

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

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

19 A To assess what?

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

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

FOMBONNE - CROSS

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

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

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

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

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

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

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

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

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

11 Q In general.

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

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

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

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

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

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

17 So at that time you could have said there is
18 20 or 25 percent of population variance which is
19 attributable to other, i.e., environmental factors,
20 but then when we look at the nonaffected cotwins we
21 found out they had what I described last week as being
22 this broader autism phenotype which is a kind of mild
23 phenotype critically associated with autism and
24 sharing the same genetic propensity.

25 When we add this broad autism phenotype then

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

9 If that is the case the question is what it
10 is. It's not very likely in the sense that, you know,
11 twins compared to siblings DZ twins, fraternal twins,
12 have more of the same environment than siblings
13 because they grow up in the same pregnancy, same womb,
14 et cetera. So we would predict that if there were
15 environmental factors, particularly those occurring
16 during pregnancy, they are more shared by fraternal
17 twins than by siblings.

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

25 Q But certainly that issue is as open as the

FOMBONNE - CROSS

1 purely hypothetical one that the only reason it's not
2 100 percent is that we don't have the measuring
3 technology to get there so that the door is open for
4 an environmental contribution. I think there's even
5 been testimony by other Respondent experts.

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

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

17 A Yes. No, I agree.

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

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

22 MR. MATANOSKI: Your Honor, before the next
23 question I permitted the questioning to go on about
24 genetics to go on for quite a while hoping that there
25 would be some tie to it at some point to epidemiology,

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1 so if there's going to be a proffer that this is going
2 to be tied to epidemiology I'll be happy to let it
3 continue, but if there's not then I think he's beyond
4 the scope of direct, which was fully limited to the
5 discussion of epidemiology.

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

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

22 It simply is I think as a practical matter
23 impossible to untangle the threads of causation that
24 are posited in this case from the epidemiology
25 testimony, and there will be questions in epidemiology

FOMBONNE - CROSS

1 about confounding and environmental contributions,
2 what has been looked at, what hasn't been looked at,
3 how that fits into the reliability and the specificity
4 of epidemiology.

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

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

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

18 BY MR. POWERS:

19 Q Now, one of the issues that you spoke about,
20 and let's talk directly about epidemiology and
21 causation, and particularly the genetic causation.
22 Because I didn't see them in the presentation today
23 had there been any epidemiological studies in the
24 United States looking at the occurrence of autism in
25 genetically high risk populations, that is within

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1 families who have people with an autism diagnosis?

2 A Yes.

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

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

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

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

23 A No. I don't recall if they did or not.
24 Just to answer further your question there are ongoing
25 studies, I mean, groups of U.S. investigators which

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1 are looking at the risk of autism in siblings, and
2 they use longitudinal studies for that. There is a
3 BBC network to which many U.S. contributors are
4 associated now.

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

9 A Yes.

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

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

22 Q Exactly, but the initial conclusion that
23 this was happening was a series of case studies, and
24 the epidemiology came later really more as a
25 confirmation of what had been revealed in the series

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1 of

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1 case studies, correct?

2 A Unless you do the confirmation there is no
3 conclusion.

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

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

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

24 A It's just that in medicine when you have an
25 unusual observation a case report is not informative

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1 for causation in general.

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

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

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

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

23 Q Yes, I understand. It definitely takes a
24 lot of time. I mean, probably science and law
25 together work at a pretty slow pace. You talked about

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FOMBONNE - CROSS

1 thalidomide exposure, that's a prenatal exposure, an
2 environmental exposure, that has been known to cause
3 autism. If I recall it was thalidomide exposure
4 between days 20 and 24 of the pregnancy. Is that
5 correct?

6 A Correct.

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

15 A No, it's not correct.

16 Q So there was a large cohort population
17 study, and it was that study that was then able to
18 identify these thalidomide cases that arose from days
19 20 through 24 of pregnancy?

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

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1 Q About how many?

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

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

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

22 A No, no. It's an important question. It's
23 absolutely not a diagnostic method. There is nothing
24 in the DSM or nor in ICD-10 which tells you or a
25 clinician how to evaluate a child, so it's left up to

2615A

FOMBONNE - CROSS

1 you. You can just walk in the waiting room, observe
2 the child, make up your mind, and if you have enough
3 symptoms you can score DSM-IV criteria and then reach
4 a conclusion.

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

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

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

23 A Yes.

24 Q And is that used in other countries?

25 A It is used in other countries, but in many

FOMBONNE - CROSS

1 other countries ICD-10 is the preferred diagnostic
2 nomenclature.

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

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

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

21 A It's meant to provide a common language to
22 practitioners, common diagnostic systems, across
23 countries. It's also meant to provide a common
24 reporting system for important vital statistics in
25 many countries. So it's real important. And ICD-10,

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1 unlike DSM-IV, covered a whole range of medical
2 disorders. So in ICD-10, you have one chapter which
3 is called Chapter F if I recall which is dealing with
4 psychiatric disorders. So that chapter, which is just
5 a tiny part of ICD-10, is comparable to DSM-IV, which
6 also is only dealing with psychiatric conditions.

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

9 A Yes.

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

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

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

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

23 Q So it would be Denmark, Sweden, Japan, the
24 U.K., Canada and the U.S. Which criteria does each of
25 those countries use to record their diagnosis of

FOMBONNE - CROSS

1 autism, DSM-IV or ICD-10?

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

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

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

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

23 Q And the idea would then be that there would
24 be global uniformity in your diagnostic definitions,
25 correct, so that any diagnostic conclusions that you

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1 reach, whether it's in the U.K. or wherever, can be
2 matched to other diagnostic conclusions in autism
3 anywhere in the world?

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

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

21 Q I understand the areas of discrepancy, and
22 if I recall from your expert report paragraph 29
23 discussed two studies that you cited for the
24 reliability of diagnoses across countries. There was
25 Volkmar and Filipek. I know you didn't discuss those

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1 today, but there was a 1994 study and a 2000 study.

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

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

11 Q Yes.

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

16 We collected data as early as 1988, 1989,
17 1990, and the idea was to ask various expert groups in
18 the world to rate -- basically what we were asked is
19 in our clinical practices to see autistic children the
20 way we are seeing them, collect some data, IQ data and
21 whatever we needed, but then to apply after the
22 conclusion of our clinical examination various
23 diagnostic schemes.

24 In other words, we used DSM-III, we used
25 DSM-III-R, we used the draft guidelines for ICD-10 and

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1 we used the draft guidelines for DSM-IV. Then the
2 idea was then to compare how each diagnostic scheme
3 was performing in relation to each other and in
4 relation to a gold standard, which was the clinical
5 judgment, which is always --

6 Q I'm sorry, which was?

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

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

22 MR. POWERS: Well, doctor, I want to direct
23 your attention, and maybe folks at Respondent's table,
24 since we just have paper copies of the presentation
25 today could get these up on the screen for me so that

FOMBONNE - CROSS

1 everybody can see what we're referring to?

2 BY MR. POWERS:

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

9 A Yes.

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

13 A Yes.

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

16 A Correct.

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

21 A Ten in your --

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

25 A Yes.

FOMBONNE - CROSS

1 Q So by aggregating this data and presenting
2 it as 6.6 if one looked only at the 6.6 one would have
3 no idea of knowing within these 14 subpopulations what
4 the prevalence rate actually was in each of those
5 places, correct?

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

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

14 A Correct.

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

19 A Correct.

20 Q How can one explain the difference between
21 prevalence rates based on health sources versus
22 prevalence rates derived from education sources,
23 particularly when you have a rate that is 300 percent
24 difference between say Alabama and New Jersey and a
25 completely inverted ratio of health sources to

FOMBONNE - CROSS

1 education sources? Any idea of how that might be
2 explained?

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

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

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

2625A

FOMBONNE - CROSS

1 countries as well.

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

8 A Sure. Sure.

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

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

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

2626A

FOMBONNE - CROSS

1 Q Let's look at Slide 7 if we could. Now,
2 Slide 7 as I understood it was that in Finland they
3 took a group of children between the ages of 15 and 18
4 years old and they looked first to see if you applied
5 the old Kanner diagnostic criteria what your rate of
6 autism would be, and then applied ICD-10 or DSM-IV for
7 autism as a discreet component of the broader spectrum
8 and then finally autism spectrum disorder, correct?

9 A Yes.

10 Q In doing that the rates go from 2.3 per
11 10,000 to 7.6 per 10,000, correct?

12 A Correct.

13 Q If I recall your testimony you said that the
14 generally accepted prevalence rate for autism spectrum
15 disorders that's recognized currently is roughly 60
16 per 10,000. Is that a correct statement of your
17 testimony?

18 A In population surveys recently, yes.

19 Q I was just curious looking at this slide,
20 with applying the ICD-10, which is the currently used
21 global standard, and DSM-IV it just seems that one
22 would expect to see a number closer to 60 than 7.6
23 leading to the question, what happened to the other
24 52.4 people that you would expect to see there?

25 A Well, let me explain to you a few things.

2627A

FOMBONNE - CROSS

1 The study is published in 2000, all right, and it's
2 based on a kind of registry which is existing in
3 Finland, so it's not the type of population survey
4 where you screen very actively to identify cases in a
5 particular area, it's more like this type of a
6 standard study statistical data that you have in many
7 countries, so that would in itself lead to a lower
8 figure.

9 Then if you look at the age the study is
10 published in 2000. The data might have been collected
11 in let's say 1998. So these subjects were born in
12 1970 so that they will be having a lower rate in terms
13 of at age 15 or 18 is not entirely surprising
14 considering that they were born in the early 1970s.

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

21 So whether or not they have low rate or high
22 rate in their study is irrelevant here. What matters
23 is that there is internally in that data set you can
24 see that you can have a tripling of your prevalence
25 rate by just applying different sets of diagnostic

FOMBONNE - CROSS

1 criteria, everything being equal otherwise.

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

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

9 MR. POWERS: I realize the time coming up on
10 12:25. I have a significant number of questions still
11 to ask, and I just wanted to interrupt myself here to
12 see how the Special Masters wanted to schedule today.
13 I have at least an hour.

14 SPECIAL MASTER HASTINGS: Let's go until
15 1:00 or around then if there's a breaking point
16 somewhere around there.

17 BY MR. POWERS:

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

23 A Correct.

24 Q If I recall, earlier in your testimony you
25 said that education social service referrals were not

FOMBONNE - CROSS

1 a good reliable source of prevalence data. You had
2 slides on that.

3 A Correct.

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

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

13 Q Which is incidence, correct?

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

24 We know we have this data and these trends
25 that some people claim are alarming and showing that

2630A

FOMBONNE - CROSS

1 there is an epidemic. It says well, actually now we
2 have U.S. population surveys done by the CDC which
3 give us a reasonable range for what is likely to be
4 the true population rate or something which is close
5 to that, and it gives two studies which are providing
6 a minimum rate of 34 and a maximum rate of 68, which
7 is based actually on the breakdown sheets of CDC.

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

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

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2631A

FOMBONNE - CROSS

1 So the point here is that you say anything
2 which is going up in this trend is not telling us
3 about what's happening in the population because it
4 started very low, it had to capture, but this is
5 what's happening.

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

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

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

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

25 A These are children who are in the

2632A

FOMBONNE - CROSS

1 educational system with a recognized special
2 educational need under the autism category which was
3 set up as a separate category in 1993.

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

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

22 So the fact that there are trends up are not
23 really particularly informative. There is a good
24 study by Barbaresi in the Rochester Mayo Clinic
25 registry which shows increased cumulative incidence.

FOMBONNE - CROSS

1 That's one of them.

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

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

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

25 So these phenomena are shown to contribute

FOMBONNE - CROSS

1 to the increase in the prevalence figures. I think
2 there is no doubt about that. Can we say that all of
3 the increase in prevalence is entirely accounted for
4 that? No, we cannot be sure about that. It's true
5 that the magnitude of these methods, in fact we are
6 fairly certain that in theory, it could explain it
7 all, but there is no direct demonstration that it is
8 the case.

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

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

24 Q Yes. I think it was in April there was a
25 couple of days that the IOM had these meetings here in

2635A

FOMBONNE - CROSS

1 Washington, D.C.

2 A Yes. Correct.

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

8 A Yes, that's correct.

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

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

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

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

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

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

2636A

FOMBONNE - CROSS

1 Q It's a review paper. You know, we actually
2 have it. We're prepared to introduce as Petitioners'
3 exhibit whatever the next exhibit number would be on
4 the list for Petitioners' trial exhibits. As we pass
5 that out, Doctor, since you haven't read it, you've
6 made that representation, I'm not going to be grilling
7 you, or quizzing you, on the content.

8 A Thank you.

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

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

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

23 A You want me to read it?

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

2637A

FOMBONNE - CROSS

1 A Do you want me to read it?

2 Q Not out loud.

3 A Out loud?

4 Q No.

5 A Okay. Yes, I could.

6 Q Do you agree with the statement, Dr.

7 Newschaffer's statement, about what explains the

8 historical increase in the prevalence rates is

9 accurate?

10 A Well, I mean, it's not inaccurate, but I
11 think it doesn't seem to reflect some data which is
12 more convincing in terms of showing that a large
13 proportion of the increased prevalence figure can be
14 explained by what we've discussed so far.

15 I'm going to complete my answer, just maybe
16 get one of, this one, the third one. I would like to
17 say --

18 Q On this, I was just asking because again, I
19 don't want to do any ambush type thing where I'm
20 asking you to comment extensively.

21 A You know, you're taking a paper by someone
22 who is taking a particular approach, which is
23 prospective, and I'd like to show you this one.

24 Q As you search for that slide, I will
25 perhaps, for the benefit of those who are listening

FOMBONNE - CROSS

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

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

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

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

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

25 Q No.

2639A

FOMBONNE - CROSS

1 A That this --

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

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

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

14 Mr. Matanoski: These are slides, as
15 previously, where we decided for the sake of moving
16 the presentation along, not to go through quite as
17 much information as we had available.

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

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

25 SPECIAL MASTER HASTINGS: I guess if you

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

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

8 SPECIAL MASTER HASTINGS: Go ahead, Mr.
9 Powers.

10 BY MR. POWERS:

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

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

17 A Correct.

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

22 A Yes, it's usually between 12 and 15 months
23 of age on average -- it gives, I think, the average
24 MMR immunization date in this study. It might be 14
25 months of age, I'm not sure. I'd have to check,

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FOMBONNE - CROSS

1 but it's between 12 and 15.

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

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

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

12 A Most certainly.

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

16 A Correct.

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

22 A Of ethyl mercury, yes.

23 Q Yes, so that's ethyl mercury.

24 A Good.

25 Q So it would be 150 micrograms of thimerosal,

2642A

FOMBONNE - CROSS

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

5 A Correct.

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

9 A Correct.

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

16 A In the --

17 SPECIAL MASTER HASTINGS: Taylor, you said
18 Tucker.

19 MR. POWERS: I'm sorry, Taylor.

20 THE WITNESS: Okay.

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

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

FOMBONNE - CROSS

1 BY MR. POWERS:

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

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

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

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

23 A If you say so, yes.

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

FOMBONNE - CROSS

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

3 A Yes, I believe so.

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

7 A Probably not.

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

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

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

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

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

FOMBONNE - CROSS

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

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

6 A Yes.

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

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

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

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

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

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FOMBONNE - CROSS

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

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

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

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

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

22 A No, except in special circumstances, I
23 believe.

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

2647A

FOMBONNE - CROSS

1 MMR issue, correct?

2 A Yes.

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

6 A Yes.

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

10 A From 1993, or 1992, yes.

11 Q Right. At some point --

12 A Yes.

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

16 A Correct.

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

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

FOMBONNE - CROSS

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

3 Can we have this last slide?

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

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

8 THE WITNESS: This is a new slide.

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

12 THE WITNESS: No.

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

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

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

22 THE WITNESS: Yes, it's already --

23 (Multiple voices.)

24 BY MR. POWERS:

25 Q Okay. So this is directly from the paper.

2649A

FOMBONNE - CROSS

1 It's not an additional complication?

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

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

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

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

19 Then, if one looks at 1993, 1994, that's the
20 group which was more likely to have not had
21 thimerosal-containing vaccines. In subsequent years,
22 1995, 1996, they didn't have any thimerosal-containing
23 vaccines. They only had MMR.

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

FOMBONNE - CROSS

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

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

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

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

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

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

FOMBONNE - CROSS

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

5 A Correct.

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

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

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

12 A Yes.

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

17 A Yes.

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

20 A Correct.

21 Q About here, correct?

22 A No, correct, correct.

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

25 A Correct.

FOMBONNE - CROSS

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

5 A Yes, correct, I think.

6 Q The Kaye study, also U.K.?

7 A Kaye study, yes.

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

9 A Yes.

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

14 A Yes, it's correct.

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

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

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

22 SPECIAL MASTER HASTINGS: I want to hear the
23 truth.

24 MR. POWERS: Yes, I do.

25 SPECIAL MASTER HASTINGS: Why don't we take

FOMBONNE - CROSS

1 a one-hour break at this point.

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

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

6 WHEREUPON, a short recess was taken.

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

10 OPERATOR: Yes, sir, we're here.

11 SPECIAL MASTER HASTINGS: We're back in
12 conference?

13 OPERATOR: Yes, sir.

14 SPECIAL MASTER HASTINGS: Thank you very
15 much.

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

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

FOMBONNE - CROSS

1 BY MR. POWERS:

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

10 I'd like to direct your attention to Slide
11 32 from your presentation today. For the record, this
12 would be Respondent's Trial Exhibit No. 21.

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

18 BY MR. POWERS:

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

2655A

FOMBONNE - CROSS

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

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

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

9 A No, I don't know.

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

13 A Correct.

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

17 A Correct.

18 Q That was about the same time that the DSM-TV
19 diagnostic criteria was adopted globally, is that
20 correct?

21 A Not exactly.

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

2656A

FOMBONNE - CROSS

1 A Yes, I said it, and it was published in
2 1992. DSM-IV was published in 1994. However, when we
3 were working in the field, there were draft diagnostic
4 criteria, which was widely available and used by
5 various groups of researchers, before the finalization
6 of this diagnostic criteria, and the publications of
7 the books.

8 For instance, I can tell you that I was
9 doing studies and using ICD-10 criteria as early as
10 1989. The ADI, which is the tool that we all use, was
11 using ICD-10 criteria in draft form in 1989, 1990.

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

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

20 Let's pick the date 1991 on Slide 13. Do
21 you know what diagnostic criteria were being used in
22 1991 in Japan?

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

2657A

FOMBONNE - CROSS

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

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

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

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

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

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

FOMBONNE - CROSS

1 prevalence of autism.

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

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

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

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

13 Q Sure.

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

23 Q So now you think ICD-10 guidelines, which
24 were promulgated leading up to their publication in
25 1992. If you look at this graph from 1992 moving

FOMBONNE - CROSS

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

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

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

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

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

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

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

25 So whether or not it's accurate that they

FOMBONNE - CROSS

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

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

5 Okay. Now Slide 50, this is a graphic
6 representation of the data study that you published in
7 2006, is that correct?

8 A Correct.

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

13 A Correct.

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

19 A Yes.

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

24 A Yes.

25 Q If you look at the prevalence rate for 1987,

2661A

FOMBONNE - CROSS

1 you have about 45.7 autistic people per 10,000. Let's
2 round up: just 46 per 10,000, correct?

3 A Correct, yes.

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

6 A Yes.

7 Q Okay. If you then move forward in time to
8 1994, you then look and you see that the 1994 birth
9 cohort has a prevalence rate of 98 out of 10,000,
10 correct?

11 A Correct.

12 Q Is that correct?

13 A Yes, correct.

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

16 A In which one?

17 Q 1994's prevalence rate is more than double
18 1987.

19 A Yes.

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

24 A Correct.

25 Q If I was looking at that from 1987 to 1994

2662A

FOMBONNE - CROSS

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

6 One could conclude that from just cutting
7 that off at 1994, correct?

8 A You would conclude that, but it would be
9 incorrect.

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

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

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

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

FOMBONNE - CROSS

1 the model. So it's really over the whole period from
2 1987 to 1998, you have a linear increase.

3 As I said, in terms of the ratio for I think
4 from each successive birth cohort, the alteration is
5 1.1, which suggests that it can be translated into a
6 10 percent annual increase in each --

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

12 Of course, when you graph that, you're on an
13 X and Y axis that has different data points than you
14 would if you cut it off at 1994. But my question was:
15 Why should I not assume that if you did cut it off at
16 1994, why wouldn't one see a positive association
17 between a doubling of thimerosal exposure, and a
18 doubling of the prevalence of autism?

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

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

2664A

FOMBONNE - CROSS

1 what you say. It doesn't work mathematically.

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

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

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

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

2664B

FOMBONNE - CROSS

1 rule

2665A

FOMBONNE - CROSS

1 out.

2 Q At any point, did you look at say 1987 to
3 1994 and attempt to do the linear analysis and
4 calculate a confidence interval, and a P value for
5 that?

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

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

17 The answer is: No. Whatever the way you
18 look at this data, there is no association.

19 Q Now, another question that I have looking at
20 this is: It seems as if there is a significant amount
21 of variability between the prevalence rate from one
22 birth cohort to the others, within a relatively short
23 of amount of time.

24 For example, the 1992 cohort, with a
25 prevalence of 54 out of 10,000; and then the 1994

2666A

FOMBONNE - CROSS

1 cohort, with a prevalence of basically 98 out of
2 10,000. You see it if you go year-to-year.

3 Again, I understand how you devise a
4 mathematical model, and you reach a beginning point
5 and an end point, and a linear function, that
6 describes the connection there.

7 But I'm just curious; What might explain
8 this variability in prevalence rates that you see in
9 this study?

10 A My guess is as good as yours. No, no --

11 Q But you're an epidemiologist, and it was
12 your study.

13 A Yes.

14 Q I honestly don't know.

15 A No, but it's random fluctuations, you know.
16 When you select the birth cohorts -- actually, the way
17 we count birth cohorts is somewhat imprecise, because
18 we didn't have the date of birth. So basically, it's
19 based on the classrooms, rather than birth cohort.

20 Q I'm sorry, based on what?

21 A Classrooms.

22 Q Oh, classrooms.

23 A We knew, you know, the grade. That's why we
24 knew which subjects were belonging. But we have

25 //

2667A

FOMBONNE - CROSS

1 evidence that we could infer the birth cohort, based
2 on grade. It's explained in the paper how we've done
3 that.

4 So from year to year, you can have
5 fluctuations which could be quite substantial. If you
6 look at that, you're right. There are fluctuations
7 from year to year, but the trend is very robust.

8 If you look at the confidence intervals
9 around each point estimate, and you compare to
10 adjusted birth cohort, there would be no significant
11 difference between, say, 1995 and 1996. It's not
12 significant. So these are random fluctuations --
13 because they don't really differ statistically from
14 one to the other when they are contiguous.

15 Q I have some more questions about the graph,
16 but also the study that it's describing. You say in
17 1996, the level of thimerosal in the vaccines in this
18 population went to zero. That's what that horizontal
19 line represents?

20 A Yes.

21 Q How do you know that thimerosal was
22 completely out of the pediatric vaccine supply from
23 1996 forward within your study population?

24 A Well, this data was given to me by the
25 Department of Health of, I think it was, Montreal.

2668A

FOMBONNE - CROSS

1 Montreal has a specific Department of Health, where
2 there was a doctor who knows about all that, who gave
3 me this data about the immunization schedule. I
4 checked that myself, but that's what I was told.

5 Q So now the immunization schedule, as I
6 understand it in Canada, is something that's done by
7 the provinces. Is that correct?

8 A Yes.

9 Q But the stet themselves, the immunizations,
10 the biological product that's being used, are those
11 licensed by the provinces, or are those licensed by
12 the Canadian National Government?

13 A I do not know that. I don't know. I know
14 that thimerosal has been removed from most
15 immunization programs in Canada years ago; in 1996 in
16 Quebec. The timing of that in different provinces
17 differ. I think in Ontario, it was removed and then
18 put back and removed. I don't know the details.

19 Q Do you know the details of that in Quebec?

20 A Oh, well, the details of the thimerosal
21 content are shown in the slide.

22 Q Again, that's based on what you were told by
23 somebody in the Provincial Health Services?

24 A Yes, those are the official authorities
25 which make the immunizations schedule, survey the

2669A

FOMBONNE - CROSS

1 uptake of the rest of the immunization by children.

2 It's the Department of Public Health in Montreal which

3 does that. They are serious people.

4 Q Okay. I understand. The public health

5 agency of Canada, those are serious people, also?

6 A I think so.

7 Q And the public health agency folks in Canada

8 would be the ones who know what content of vaccines

9 was licensed for use in Canada, including Quebec,

10 through 1996 and beyond, correct?

11 A Yes, and I suspect there is someone in the

12 Federal Government, an office, where you could find

13 the data for all provinces. But it's actually quite

14 difficult to find.

15 Q Right, and if there was data on the actual

16 thimerosal content of vaccines from the National

17 Government that licensed those products, if that

18 differed from what you were reported by the Provincial

19 Government, that might call into question the

20 conclusions of your study, correct?

21 A I would have to see where the difference

22 originated from. But I think it's pretty clear that

23 in Quebec, vaccinations have been thimerosal-free

24 since at least 10 years, and it's very clear. Based

25 on all sorts of indicators that the rates of

FOMBONNE - CROSS

1 autism have increased and that this increase bears no
2 relationship with thimerosal.

3 Actually, I am doing another study of that
4 kind to just replicate because people asked me to do
5 these studies. So we will have soon have data
6 replicating these same findings in a more recent
7 period of time. From what I've seen so far, the rates
8 are as high as at the end of this period; again, in
9 the thimerosal-free environment.

10 Q When do you anticipate publication of that?

11 A Not soon.

12 Q I mean, like months or a year? I'm just
13 curious.

14 A In a year, probably.

15 Q Okay. So then another question I have for
16 you is shifting subjects a little bit, but still
17 related to this study.

18 MR. MATANOSKI: On these subjects, I want to
19 be clear that your question about licensure was about
20 licensure, and not about use of vaccine, correct?

21 MR. POWERS: It's about licensure, yes.

22 MR. MATANOSKI: Okay.

23 MR. POWERS: Well, it's about licensure, and
24 then to the extent that licensure reflects what is
25 actually in use.

2671A

FOMBONNE - CROSS

1 BY MR. POWERS:

2 Q So another question I have is, the children
3 that you're tracking for the prevalence rate here,
4 these are children that went to a particular school
5 district. I think it's a school board in Montreal. I
6 think here, it's a school district. Is that correct?

7 A Yes, yes, more or less, because the school
8 boards are organized by language in Montreal. Before
9 it was religion. Now it's language. So you could
10 have in the same geographical area, a school which
11 belongs to one school board and the next school
12 belongs to another school board based on language
13 differences.

14 Q Yes, we tend to do it geographically.

15 A Yes, but it's more or less, a school board
16 which is covering the whole western part of the Island
17 of Montreal, which is a rather wealthy, affluent part
18 of the city and, therefore, we see that.

19 Q Exactly, and so it's that population that we
20 see the red line and the squares tracking the
21 prevalence rates, correct?

22 A Yes, correct.

23 Q Now my understanding is that you then were
24 looking at vaccine coverage rates, also.

25 A Yes.

2672A

FOMBONNE - CROSS

1 Q Or uptake rates -- I've heard those terms
2 used interchangeably. But basically, it means how
3 many people within your study population are actually
4 being exposed to the vaccine. Now your uptake group
5 or your exposure group, was that group of children
6 from the exact same geographic location in Montreal
7 that your prevalence data comes from?

8 A No.

9 A Where was it from?

10 Q It was from Quebec City. There was a group
11 there, which is called the National -- something.
12 It's a public health organization in Quebec City,
13 which conducts repeated surveys amongst children that
14 are, I think, four or five years old, which allows
15 them to calculate regularly. So every year we do
16 that, we calculate which is the proportion in that
17 population, which is currently vaccinated, according
18 the full immunization schedule.

19 So the proportion of MMR coverage, which I
20 used on the previous slide, is derived from this
21 particular study. So the trend for MMR use is
22 originating from a different area, because there is no
23 data on this particular area, that we could map them
24 directly to the rates.

25 There are some other studies that could have

2673A

FOMBONNE - CROSS

1 been used in Montreal, which are functional surveys.
2 But in terms of estimating a trend with regular
3 surveys, which I don't know the same methods, that was
4 the only settled data.

5 THE WITNESS: So I want to make sure that
6 I'm clear. Because when I was looking at this, I was
7 assuming, and it sounds like I was incorrect -- I was
8 assuming that the prevalence rate that you're tracking
9 within a population is within the same population that
10 the exposure information comes from.

11 But that isn't correct here. These are from
12 two different places geographically, what, 250
13 kilometers apart; Quebec City and Montreal.

14 A How much?

15 Q I'm guessing 250 kilometers?

16 A I think you're correct.

17 Q So we have a prevalence population that is a
18 physically different population than the exposure
19 population, correct?

20 A Yes, but we had data from the local area
21 where the study was done. Yet you could say, these
22 are ecological aggregated data. So it would still
23 leave open the question as to whether or not children
24 with autism were actually exposed to this medication.

25 So that's the limitation of all ecological

2674A

FOMBONNE - CROSS

1 analysis. Often people use what they can to estimate
2 trends, and this is the best information that we have
3 to look at trends in MMR use in Quebec; extrapolating
4 from the Quebec City repeated surveys to the whole of
5 the population. That has some pitfalls, but it's also
6 the best data that we could obtain.

7 Incidentally, the downhill trend in MMR
8 coverage is probably rightly estimated. Because there
9 has now been a measles outbreak recently in Montreal
10 for the last three weeks. So clearly, it has gone
11 down in recent years.

12 Q Now you mentioned that data aggregation and
13 looking at analogous data on exposure is the best
14 information that you had in this instance.

15 So when I hear that, it makes me believe
16 that for the physical Montreal cohort, what you're
17 saying is that their actual exposure data does not
18 exist, and you therefore had to use exposure data from
19 Quebec and aggregate it province-wide to come up with
20 your best estimate for the Montreal exposure. Am I
21 understanding that?

22 A That's the design of the study. It's
23 ecological and that's what it is. Yes, you're
24 absolutely correct. That's what we did.

25 Q But it would be better data to use, if

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FOMBONNE - CROSS

1 Montreal data existed, so you had the actual exposure
2 rates for the actual children whose outcomes you're
3 tracking. Let me finish. That would be better than
4 aggregate data from another city, 250 kilometers away.
5 Is that a fair statement?

6 A Not necessarily, so -- there are factors
7 which influence vaccination uptakes which are, in
8 particular, social class or the proportion of
9 immigrants in a particular area.

10 This area, the western part of Montreal, is
11 very stable. It's a very wealthy population. It's an
12 Anglophone population. Our hospital, the Children's
13 Hospital of McGill, does prevail - services the
14 population for pediatric care.

15 I can tell you from all the studies which I
16 have done, where we had actually in my autism service,
17 data about individual vaccination records, of children
18 with ASDs, included in other studies, where the uptake
19 of vaccinations was 100 percent or 99 percent.

20 Q And I totally understand the uptake; that
21 there might be a grade in uptake rates.

22 A What I mean is, I'm confident that the
23 children who have PDDs in those studies; where we
24 didn't have individual immunization records, because
25 that's a limitation of the study, we're very likely to

2676A

FOMBONNE - CROSS

1 have followed the official immunization schedule,
2 because of the nature of the population from which
3 they arise.

4 Then the Quebec City data, in terms of
5 vaccine uptake, coming from sort of also a rather
6 affluent area; so middle class, or lower middle class.
7 So it's probably not a bad trend to use to apply to
8 our Western part of the island.

9 If you were to take Montreal data for
10 instance in that particular study, in the East part,
11 it would tap into very impoverished populations, or
12 areas where there are large proportions of immigrants,
13 where vaccine uptakes would be very different and not
14 applicable to our particular situation.

15 Q Right, and I understand the difference
16 between uptake rates from one location to the other.
17 But the difference that you're looking at here, given
18 an uptake rate, is what your prevalence outcome is.

19 So even though your uptake rates might vary
20 geographically based on the social-economic factors,
21 within a population where you define the uptake, any
22 association with the outcome should be consistent. I
23 mean, it's not as if people are going to have
24 different prevalence rates, based on where they live.
25 Once you've got the accurate data on uptake, it should

2677A

FOMBONNE - CROSS

1 make a different -- the socioeconomic, and sort of
2 participation bias factors, right?

3 A I'm not entirely following your argument.

4 Q I didn't mean to make it an argument. I
5 meant to make it a question.

6 A No, no, no.

7 Q So let me rephrase it for you then. I
8 understand that there are reasons why, from one
9 physical location to another, the uptake rate or the
10 vaccine coverage rate, might be different. I
11 completely understand that.

12 But within a population, those socioeconomic
13 and other factors shouldn't make a difference, given
14 the uptake in that population and prevalence. That
15 relationship should hold constant across any
16 population, correct?

17 A I think you use "population" in a different
18 sense. Are you talking about "sample"?

19 Q Sample, sample.

20 A Okay. That's different. So your point is
21 to say, in a given sample, if you have on that sample,
22 on that population from which a sample has been
23 selected, if you know what is the uptake in terms of
24 various immunizations, yes, you could apply it.

25 Q Okay.

2678A

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1 A Yes, of course.

2 Q Okay.

3 A Can I say something in relation to what we
4 were discussing?

5 Q Is it in response to a question of mine?

6 A One of your questions.

7 SPECIAL MASTER HASTINGS: I think, Doctor,
8 it turned out, when you understood that question, it
9 was very simple and obvious; yes, of course.

10 THE WITNESS: Okay.

11 MR. MATANOSKI: I'm not sure that he did
12 understand the question, because he answered uptake
13 versus prevalence. He answered uptake. If you look
14 at the sample, yes, and I'll know what the uptake is
15 in the sample. But I think the question went to
16 prevalence, and why not use prevalence in the same
17 sample?

18 SPECIAL MASTER HASTINGS: Okay. My point
19 was simply going to be, sometimes we lawyers ask
20 questions, Doctor, that you're maybe looking for more
21 to it than there is. Sometimes, we're just trying to
22 confirm. We summarized what you just said in a short
23 way, to make sure we're under-
24 standing it; and sometimes, it's a simple yes, you
25 know.

2679A

FOMBONNE - CROSS

1 THE WITNESS: Okay.

2 SPECIAL MASTER HASTINGS: So don't read too
3 much into the question. We may, you know, get done a
4 little earlier.

5 THE WITNESS: Okay.

6 BY MR. POWERS:

7 Q And indicating that that was, in fact, the
8 case, I'm going to move on to another discussion here.
9 Just a question I had, and we can pull this slide
10 down. I don't have any more questions about that
11 slide or any others immediately here.

12 Are you aware of any epidemiology that
13 explored a potential association between regressive
14 autism as an outcome, and a combined thimerosal MMR
15 exposure?

16 A No, I don't think that has been looked at,
17 in as specific a way that you mentioned. There are
18 data which contest this hypothesis.

19 Q I understand that, and I'm trying to keep it
20 to the very specific published studies. I take it
21 from your answer there, although there may be data out
22 there that somebody might want to do a study on, as of
23 right now the answer would be no.

24 A I think in terms of published studies, I
25 don't think there is any study which has looked at the

2680A

FOMBONNE - CROSS

1 combination of the two exposures in relation to
2 regressive autism. But we can use some of the
3 existing data to make sense of this question.

4 Q Then the next question is, are you aware of
5 any published epidemiology that explored an
6 association between regressive autism and the MMR,
7 aside from any thimerosal-containing vaccines
8 considered in the mix?

9 A Yes.

10 Q And what study would that be?

11 A Between regressive autism and MMR?

12 Q Right.

13 A Well, all the studies have been presented
14 this morning.

15 Q We talked about a number of those. Would it
16 also include your 2001 study?

17 A Yes, that will be one study; the study by
18 Taylor in 1999 in the U.K. gives a lot of data on
19 regression and MMR exposure. Two Japanese studies
20 provide some data on that.

21 Q And looking specifically at the regressive
22 presentation?

23 A Yes, and no study was positive.

24 Q I'm sorry?

25 A No study showed an association between an

2681A

FOMBONNE - CROSS

1 MMR exposure and regressive autism.

2 Q Correct, and are you familiar with the
3 Cochran Collaboration?

4 A Yes.

5 Q I'm sure that you're aware that they did a
6 review article in 2005, that looked at the studies,
7 and sort of did a review of epidemiology on studies
8 examining vaccines and measles, mumps, and rubella.
9 Are you aware of that review?

10 Q Yes.

11 A Are you aware, in that review, that they
12 describe your study as having a number of possible
13 biases in the study; and that number was so high that
14 interpretation of the results was difficult. Do you
15 recall if that was their description?

16 Q Yes, and I would like to comment on what
17 they actually said, because this is cited out of
18 context. The preceding paragraph, I think, describes
19 the studies, the design, the findings; and then there
20 is a sentence, which is completely unsubstantiated.

21 There are no comments about what roles, what
22 biases, they actually refer to. It's very hard to
23 actually pinpoint what they actually mean by that; and
24 they comment on all our studies with the bias, the
25 instant review, which is, how should I say, naive.

2682A

FOMBONNE - CROSS

1 I said in some words, you can say, for each
2 study, that there are biases and issues. That's fine.
3 But what is less acceptable? I think, as you saw,
4 it's flawed or is biased, without giving me any
5 substance.

6 Just to follow-up on that, because I know
7 this particular sentence, because it has been used on
8 the web by those people, so I know it. It doesn't
9 impress me.

10 I can tell you, the study, which was
11 published in 2001, has been widely quoted. If you
12 look at the study done by the NIH-funded investigators
13 from the U.S. recently, looking precisely at the
14 regressive phenotype and the Wakefield phenotype, they
15 actually set up to do the study to follow-up on my own
16 initial study, to try to replicate the findings; and
17 they were quite complimentary about that study.

18 Q I knew you would take issue with it. But I
19 just wanted to hear your comments on it, because I had
20 run across that.

21 So I want to shift gears. We've been
22 talking a lot about MMR, and we talked a little bit
23 about some of the studies that you mentioned in your
24 presentation today, in your report and in your direct
25 testimony, on the thimerosal issue.

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2683A

FOMBONNE - CROSS

1 There is one, the Verstraeten Study. That
2 was the article published in 2003 in Pediatrics, and
3 Thomas Verstraeten is the lead author. You're
4 familiar with that article, I assume?

5 A Yes.

6 Q One of the things that struck me, and I just
7 want to get your comments on this -- what struck me is
8 that if one looks at that study, and looks at the
9 number of actual cases of autism that were identified
10 in that study population, one comes with a prevalence
11 rate of roughly 20 per 10,000.

12 You'll recall, one HMO had something like
13 202. I mean, we can put the numbers up. But if you
14 recall as correctly as I do, it's roughly 20 out of
15 10,000. Does that sound about right?

16 A In that HMO?

17 Q Well, overall, with the three HMOs, if you
18 looked at the total number of kids, your denominator,
19 and looked at the total number of "Ns" which is the
20 numerator they're looking for with autistic diagnosis,
21 it would be roughly 20 out of 10,000. Does that sound
22 about right?

23 A I would have to check. But if you've done
24 that, you're falling in the same trap that you
25 described this morning regarding the CDC data.

2683B

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1 Because you

2684A

FOMBONNE - CROSS

1 would be pulling together data from HMOs where the
2 prevalence --

3 Q But you're anticipating questions that
4 aren't coming, because I actually agree with you on
5 some of these things.

6 A Okay.

7 Q That's why I want to explore your opinion.
8 So let me ask the questions, and we'll save some time.
9 So the question is a simple one. Do you recall 20 out
10 of 10,000 being roughly the prevalence rate?

11 A No, I'll have to look at the paper.

12 SPECIAL MASTER HASTINGS: Well, he'll give
13 you the paper, if you want to look at it.

14 THE WITNESS: I recall there were 202
15 children with autism HMO B, 20 in HMO A --

16 SPECIAL MASTER HASTINGS: Again, the
17 question was, do you recall. You said no. You've
18 answered the question.

19 THE WITNESS: Okay.

20 BY MR. POWERS:

21 Q And since you don't recall, we're going to
22 show you the paper --

23 A Okay.

24 Q -- and we can just cut to it. Okay. Well,
25 thanks to Mr. Shoemaker, we have the paper up. I know

FOMBONNE - CROSS

1 this is an exhibit. So this is Petitioner's Exhibit
2 150.

3 SPECIAL MASTER HASTINGS: No, I think it's
4 Respondent's Exhibit P, at Tab 150.

5 BY MR. POWERS:

6 Q Okay. So let's look at page 1043.

7 A Yes.

8 Q We want to look at the number of cases of
9 autism that are present. If you look at HMO A on this
10 table, down at the bottom, you have autism. You have
11 autism that occurs at the column on the left under HG.
12 Those are the ranges of exposures.

13 But basically, they're looking at two
14 different ranges there. So you have a total number of
15 autistic cases in HMO A of 20. Is that right; twelve
16 and eight?

17 A Twenty-one.

18 Q No, it would be twenty; twelve and eight.

19 A What about the one?

20 Q Oh, and then the one, yes. I'm sorry, so
21 twenty-one. Yes, I know, number one is ADD. So we're
22 just looking at autism, which were the last two.

23 MR. MATANOSKI: No, it's autism 0275, 87
24 through 162.

25 MR. POWERS: So it's twenty-one.

2686A

FOMBONNE - CROSS

1 BY MR. POWERS:

2 Q Then if you look over at HMO B, you've got
3 37, 148, and 17. That's 192? So that would be the
4 numerator. Then the total number of children in each
5 of those HMOs would be the denominator.

6 If you look at the text, and that's why I'm
7 trying to find it in the text, you would have in HMO B
8 the total number of children that are included in HMO
9 B. That would be on page 1031. Do you see the boxes?

10 Then at the very bottom, it says, "Final
11 Cohort." For HMO B, you've got a Final Cohort of
12 110,833 children, and we know that you had 192
13 autistic diagnosed children in that cohort, correct?
14 That's the number we already figured from the other
15 page.

16 A It's not on mine. I have more than you.

17 SPECIAL MASTER HASTINGS: I think you may
18 have been wrong in your addition. I've got 202,000.

19 MR. POWERS: You know, that's what I had
20 before; yes, 202.

21 THE WITNESS: It's 202,021.

22 BY MR. POWERS:

23 Q That actually makes the math somewhat easy.
24 Because actually, 21 out of 13,000 would actually be a
25 little bit less than 20 out of 10,000, in HMO A?

2687A

FOMBONNE - CROSS

1 A Yes.

2 Q And 202 out of 110,000 would be roughly 20
3 out of 10,000 in HMO B, correct?

4 A Yes.

5 Q So that math exercise is just to get to the
6 point that if you look at the population here, you are
7 looking at a prevalence rate of roughly 20 out of
8 10,000.

9 Now my understanding from your earlier
10 testimony is that you would expect an actual
11 prevalence rate more on the line of 60 out of 10,000.
12 Is that correct? That's typically what you would
13 expect to see in a population; 60 out of 10,000?

14 A Yes, based on recent estimates, yes.

15 Q So in this study, it appears fair to say
16 that there's an under-counting of autistic children in
17 this sample, correct?

18 A No, I can't say that unless I know exactly
19 what they did in terms of subject selections. It
20 depends. It's a cohort study, as I recall. So the
21 number of cases identified would be closely tied to
22 the length of observation in the population. So that
23 could reflect that, and just that.

24 Q And the numbers could be lower than what one
25 might expect, based on your general prevalence

2688A

FOMBONNE - CROSS

1 estimates, because it's automated data generation.

2 It's not case ascertainment.

3 A Yes.

4 Q It doesn't take into account diagnostic
5 substitution, and all of the things that you talked
6 about before that might drive that number up, correct?

7 A Yes, but the goal of the study is not to
8 assess prevalence.

9 Q I understand. I understand. But that
10 wasn't the question. I just want to make sure that
11 we're looking at the same numbers and talking about
12 the same thing here.

13 Now also, if you look at the text of the
14 study, you might remember that the average age of
15 diagnosis is 44 to 49 months. Is that an average age
16 of diagnosis for autism that you find in your
17 experience?

18 A It's very consistent for studies done for
19 children born, I suppose, in the mid-1990s. That
20 would not be unreasonable. That would be just below
21 age four. In recent studies we've done in the U.K.,
22 the age of diagnosis was, on average, 36 months.

23 Q That's the number that I was remembering.
24 But that's based on criteria methodology that you're
25 using now, as opposed to what was being used 10 years

2688B

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1 ago?

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1 A Yes, I mean, this is not really inconsistent
2 with many other center's experience.

3 Q This study, it purports to look at a
4 relationship between thimerosal exposure and adverse
5 neurological outcomes, particularly ones that are
6 identified by ICD code, correct?

7 A Correct.

8 Q And in this study, the study design required
9 that at least 50 cases of autism be identified within
10 one of the HMOs for any statistical analysis to be
11 done relating it to vaccine exposure, correct?

12 A Correct.

13 Q Out of the three HMOs that were used, only
14 one of those HMOs had a number "N" of autism diagnosed
15 children large enough to do an associational
16 assessment with thimerosal exposure, correct?

17 A My understanding whether they used two HMOs
18 first as screening to look at associations between
19 TCVs and various outcomes. So they used A and B.
20 They couldn't find enough cases in A, which was
21 therefore an uninformative for the autism analysis.
22 They had enough cases in B, 202, to look at the
23 relationship and found no association.

24 Therefore, when they went to HMO C, they
25 didn't really pursue that, because it was not a

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FOMBONNE - CROSS

1 positive association in B.

2 Q Well, actually, with HMO C, they selected an
3 HMO with a population that was several times lower
4 than the population in HMO B. That's what you see
5 that just got blown up on the screen there.

6 So when they added C, again, you add another
7 HMO, where your N value; that is, the number of
8 autistic children, doesn't reach the level 50 that you
9 would need to associate with the vaccine exposures,
10 correct?

11 A I just need five minutes to look at this.

12 My understanding of their design is that
13 they used HMOs A and B as a first pass, and they were
14 aiming at using HMO C as an independent sample to
15 confirm association which had been found in HMO A and
16 B.

17 So as far as autism is concerned, HMO A was
18 not even analyzed because there were too few cases,
19 which is logical and was in line with their data
20 analytic strategy. In HMO B, there was no association
21 between autism and thimerosal containing vaccines.
22 Therefore, this association was not even pursued,
23 because there was no attempt to confirm something
24 which was not even there.

25 Q Do you have any idea, given the size of

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FOMBONNE - CROSS

1 these cohorts in each of the HMOs, 110,000, 16,000,
2 13,000 -- I mean, we're looking at -- and I hope I'll
3 not make another math error here -- close to 140,000
4 children in there.

5 A Yes.

6 Q You would expect that, given a rate of 60
7 per 10,000, you would have many hundreds of autistic
8 children that would be captured in this study,
9 correct? That would be your expectation, based on
10 what you think the actual prevalence rate in
11 populations at this time was?

12 A No, I would not expect that in such a data
13 set.

14 Q In such a what?

15 A In such a data set that you would have as
16 many children that you would predict, based on
17 population surveys. Population surveys are different
18 types of studies. They are aiming and estimating the
19 magnitude of the problem, the prevalence. They have
20 their own method, as they come out with figures to
21 estimate these numbers.

22 This is a data base or data set, which is
23 available to do research. But we know that all
24 existing data sets have recording problems. You would
25 not use the VSD database to estimate prevalence.

2692A

FOMBONNE - CROSS

1 So if your question is, is that lower prevalence in
2 the VSD study indicating work flow, no. It's
3 something that you would predict.

4 In addition, for their purpose, which was to
5 look at whether or not exposure to TCV increased the
6 risk of autism, you know, whether or not they captured
7 100 percent of the cases of the population or just 20
8 percent is irrelevant, as long as there is no
9 differential selection bias; meaning by that, that you
10 assume that you cannot reasonably expect that children
11 who are in these studies are representative of the
12 pool of autism cases in the population, which is the
13 target population.

14 Therefore, the odds of exposure to TCVs in
15 these autism cases, even though it might not be the
16 full autism case studies, is probably adequate and
17 represents well what is happening in the whole
18 population of autistic subjects. Therefore, there is
19 no bias.

20 Q Yes, so completely aside from bias though,
21 it's not irrelevant how many autistic subjects you
22 capture. Because having a larger N is going to give
23 you more power. It's going to give you more to work
24 with, when you're looking at effects. I mean, that's
25 true, isn't it?

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1 A That's true. A larger N, a larger sample
2 size would

2693A

FOMBONNE - CROSS

1 give you more precision to estimate any types of
2 association.

3 Q Right.

4 A In that case, there is no association. So
5 even with a larger N with autism, they would have no
6 association.

7 Q But that's circular.

8 A No.

9 Q Now that's the post-hoc reasoning that
10 you're making the conclusion that given a small N
11 relative to the size of the population, and a small N
12 compared to what you think really would exist in
13 there, the 60 out of 10,000 -- if you had that higher
14 N, you would have more precision. You've already said
15 that.

16 But you're saying in a circular way, aren't
17 you, that you don't have to do that, because you know
18 ahead of time that there's no association? That seems
19 circular.

20 A I certainly didn't say that. I think you
21 don't understand the difference between a statistical
22 power sample size on the one hand, and estimation of
23 associations in an epidemiological study.

24 When we do a study like that, what we look
25 at is the point estimate of the association, the

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FOMBONNE - CROSS

1 relative risk, the odds ratio. That's the measure of
2 association. That's what matters.

3 If it's close to one on a small sample or a
4 medium sample, it's unlikely that you have missed a
5 very strong association which would be there in the
6 nature, okay? Maybe 1.2. It could be 0.8. But if
7 it's close to 1, it's likely that there is not much
8 association.

9 The sample size comes in in augmenting the
10 precision of your estimate of association. So instead
11 of having 1.0 with a confidence interval ranging from
12 0.6 to 1.9, if you double the sample size, you would
13 have still 1.0 because there is no association. But
14 you have a confidence interval of 0.8 to 1.4. So
15 that's what you gain with incremental samples. You
16 increase precision. You reduce the confidence limit of
17 your estimate.

18 But what matters, in terms of assessing
19 association or assessing if there is bias or not, is
20 looking at the point estimate, which is the value of
21 the relative risk or the value of the odds ratio.
22 That's what all counts.

23 Q Yes, and I understand the concept of odds
24 ratios and confidence intervals. But particularly in
25 a study like this where exposures are stratified, you

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1 do not have a zero group. Because remember, this
2 study is looking at the differences in outcomes, based
3 on the smaller versus larger exposures.

4 So when you have these exposures that happen
5 at 25 microgram intervals in real life via
6 immunization, you take away the zero exposure. You
7 stratify by grouping these together. If you had more
8 Ns to work with, you could break that stratification
9 out some more, couldn't you? You would have more Ns
10 to look at, to compare against exposure levels, and
11 that might give you more information.

12 A Could you be more specific about what you
13 mean? Because it's not entirely clear. If you have
14 more Ns, you could do what.

15 Q If you had a study that had generated more
16 autism cases, more Ns, and then we're looking for
17 effects, there would be more. There's a possibility,
18 with that bigger N, that you would be able to get more
19 dose-specific associations, assuming that they existed
20 at all?

21 A No, no, that's not the way it works. You
22 would have more, assuming that the autism cases which
23 are in that study have been randomly selected to
24 represent the pool of autism cases which were
25 available or should have been available with this

2695B

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1 population. Then by

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1 adding more cases of autism, you would not change the
2 trend or the level of association. There would be
3 still no association. There would be just more
4 precision in how the lack of association shows. It
5 would not affect that.

6 Because this study, in any series of cases,
7 200 cases gives you a relatively high number. If they
8 are well chosen, there is no systematic bias in the
9 selection of these cases. These cases represent the
10 distribution of exposure in the autism population.
11 Therefore, you can estimate association on different
12 levels of exposure, and you would not gain much. You
13 would just gain increasing precision by adding more
14 cases. It would change.

15 Just to make it clear, it would only change
16 if you had selected children in the first phase and
17 first phase, which would be systematically different
18 from those which would be left out, and there is no
19 evidence of that.

20 Q Yes, so selection bias, it's not
21 disparaging. It's not nefarious. You know, you're
22 trying bias against somebody. It's a technical term,
23 right, selection bias?

24 A Yes, sure, yes, it would be that
25 participation

2697A

FOMBONNE - CROSS

1 in the study is actually related to the exposure
2 status.

3 Q Right, and then certainly, any exclusion
4 criteria that were applied to potential members of the
5 cohort, exclusion criteria is going to affect
6 ultimately the outcome of your study, correct?

7 A Yes, that would be one way by which some
8 bias could occur. Also, it's a way to control bias.

9 Q Right, and it could cut both ways.

10 A Sure.

11 Q I mean, bias could be introduced or bias can
12 be controlled for, and applying exclusionary criteria
13 is one way to do that.

14 A Yes, I agree.

15 Q Now this study I have seen cited for the
16 proposition, that it is a negative study, that it
17 disproves a causal connection between thimerosal-
18 containing vaccine and autistic and other neurological
19 outcomes. Have you seen the study portrayed that way,
20 as a negative epidemiology?

21 A Yes, I think most institutes or committees
22 who have reviewed the study have found it to be a
23 negative study.

24 Q And you're aware that the author of the
25 study, Dr. Verstraeten, has somewhat of a different

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FOMBONNE - CROSS

1 opinion about whether it's a negative study, from what
2 you just described? I'm just curious, do you know Dr.
3 Verstraeten? Have you ever met him?

4 A Not at all.

5 Q Have you ever talked to him about this study
6 over the phone or anything?

7 A Never, never.

8 Q Okay. Are you familiar with a Letter to the
9 Editor of the Journal Pediatrics that Dr. Verstraeten
10 wrote in 2004?

11 A I think I've read it, but I forgot.

12 Q I'm sorry, you read it?

13 A I read it, but I will need to read it again,
14 if it's important.

15 Q Well, I think it is important on this issue
16 of, is it a negative study or not. We'll see if we
17 can pull it up here.

18 SPECIAL MASTER HASTINGS: There is a copy of
19 it in the record already, isn't there? Does anybody
20 have the citation for the record handy?

21 MR. POWERS: At the motion to compel
22 hearing, Petitioner said it would have been
23 Petitioner's Exhibit 21.

24 SPECIAL MASTER HASTINGS: All right. But
25 it's not in the record of this Cedillo case?

FOMBONNE - CROSS

1 MR. POWERS: We do have copies, if you want
2 it filed here in this case.

3 BY MR. POWERS:

4 Q Since we're obviously having trouble getting
5 it up electronically, Doctor, I've got a copy of it
6 for you here.

7 A Okay.

8 Q We can leaf through it a little bit.

9 A Thank you.

10 SPECIAL MASTER HASTINGS: All right. so
11 we'll make this Petitioner's Trial Exhibit 16.

12 (The document referred to was
13 marked for identification as
14 Petitioner's Trial Exhibit
15 No. 16 and was received in
16 evidence.)

17 BY MR. POWERS:

18 Q Doctor, it looks like you're doing it, but I
19 was going to ask you, take a moment to read that.
20 Then if you could just look up when you're done, I'll
21 just have a couple of questions.

22 A You want me to read everything?

23 Q I think it's pretty short, if you just want
24 to read that, or just have it refresh your memory. I
25 just have a couple of quick questions.

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1 A Yes, okay.

2 Q Okay. So again, this is for people who
3 don't have it in front of them. It's a one page
4 Letter to the Editor of Pediatrics that Dr.
5 Verstraeten wrote. He wrote this in Belgium, where we
6 was working for Glaxo, after having left his two year
7 fellowship at the CDC.

8 In this article, at the top of the second
9 column, he expresses surprise that his study is being
10 interpreted now. His words are, "Surprisingly,
11 however, the study is being interpreted now as
12 negative by many, including the anti-vaccine
13 lobbyists."

14 He goes on to say, "The article does not
15 state that we found evidence against an association,
16 as a negative study would. It does state, on the
17 contrary, that additional study is recommended, which
18 is the conclusion to which a neutral study must come."
19 Do you see where I'm reading?

20 A Yes.

21 Q So it would be fair to say that the author
22 of the study has a different opinion about whether
23 it's negative than what you were just reporting your
24 understanding to be, correct?

25 A Yes.

FOMBONNE - CROSS

1 Q The author of this study describes it as a
2 neutral study that warrants further study.

3 A Yes.

4 Q In fact, as I understand, the CDC -- and if
5 you don't know, you can tell me -- the CDC, as I
6 understand it, has initiated, triggered in large by
7 Dr. Verstraeten's study in 2003, at least two case
8 control studies; one looking at thimerosal exposure in
9 neurological outcomes, and another looking at
10 thimerosal exposure in autism, particularly. Are you
11 familiar with that work?

12 A I've heard about the case control studies.
13 I don't even know at which stage it is, if it's done
14 or not. But I know there is ongoing work on that.

15 Q Okay. And I was just trying to find out
16 from you, have you participated in the design of those
17 studies?

18 A No.

19 Q Do you anticipate sitting on a peer review
20 panel for any journal that might be looking at those
21 studies?

22 A That's likely to be the case, yes.

23 Q Do you have any idea of what journal you
24 might be sitting on that would review?

25 A As a reviewer.

2702A

FOMBONNE - CROSS

1 Q Yes.

2 A I review for so many journals. You know,
3 it's the kind of study which might likely come to me
4 as a reviewer, but I don't know.

5 Q But there's nothing coming your way right
6 now, is that correct, on either of these case control
7 studies?

8 A No, no.

9 Q Okay. And as I said, I just had a couple of
10 questions on that letter, but I did want to discuss it
11 with you.

12 So, Dr. Fombonne, in hearing your testimony
13 and looking at the charts and the graphs that you
14 presented, the impression I'm left with is that any
15 reports of an increased incidence of autism in the
16 population, you believe to be an artifact, so to
17 speak, of better case ascertainment, wider diagnosis,
18 expanded diagnostic criteria, all of those things that
19 you've described in detail. Is that a fair summary?

20 A Again, it's not that I believe, just for the
21 sake of believing. I'm open to see what the evidence
22 shows. I think when you see trends of either
23 direction, you have a duty before you interpret them
24 as signaling a change in the incidence of this
25 disorder, to rule out alternative explanations, as

2702B

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1 well I've

2703A

FOMBONNE - CROSS

1 been trying to do.

2 When you do that, in all published studies,
3 be they prevalence studies or incidence studies, none
4 of the existing data can be interpreted as positively
5 showing an increased incidence, controlling for other
6 factors.

7 Because most studies do not control for
8 factors of change in diagnostic criteria, and the
9 current view of many, many people is that unless we
10 can generate new studies, looking at the incidence
11 over time in ways with designs which adjust for change
12 in case definition and ascertainment, we won't be able
13 to address this question from existing data.

14 Q And maybe to put a finer point on it, I have
15 the impression that whenever there has been an
16 allegation of either the MMR or thimerosal-containing
17 vaccines, the introduction of those or the increased
18 use of those, whenever there is an allegation that
19 that is leading to a rise in the incidence of autism,
20 your response is generally that it doesn't. Because
21 any rise that you see out there is, again, the
22 artifact of the expanded diagnosis and case
23 ascertainment, and diagnostic substitution, correct?

24 A It's more complicated than that. I mean,
25 the claims of the rising rates of autism have been

2703B

FOMBONNE - CROSS

1 made in the

2704A

FOMBONNE - CROSS

1 context of this vaccination hypothesis. But there are
2 also other factors that as we discussed, changing
3 diagnostic systems. So how you tease what does, what
4 is a scientific question which requires empirical
5 testing of competing models to explain the same
6 observational data.

7 So far, there is no data which is
8 convincing, which can really rule out alternative
9 explanations, as I said before. In fact, it's not
10 only looking at the rise. Because when we have like a
11 discontinuation in exposure to particular
12 vaccinations, you can still see the rise going on.

13 So it's quite convincing in some ways, that
14 a lot of this rise, if not all of it, has nothing to
15 do with vaccination. Otherwise, when in a country,
16 TCVs are discontinued or MMR is discontinued, you
17 wouldn't see the rates of autism continue in their
18 trend up.

19 Q I think that when you're just talking about
20 hits on something that, to me, it sounds almost like
21 trying to have it both ways. If there is an
22 allegation that you have a rise that is caused by or
23 is associated with exposures like thimerosal or the
24 MMR, the rise is explained away by diagnostic
25 artifact.

2704B

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1

But when you fail to see a drop in rates

2705A

FOMBONNE - CROSS

1 after the exposure is removed, you say, well, that's
2 proof that the exposure wasn't causing anything.

3 Well, really, you would expect to see,
4 because of the diagnostic substitution, case
5 ascertainment, wider diagnosis, earlier diagnosis,
6 more attention, all of that, you would expect to see
7 prevalence rates continue to rise. So it just seems
8 like those are trying to have it both ways, doesn't
9 it?

10 A No, because you are using a type of analysis
11 which is basically ecological in your reasoning. You
12 are trying to compare trends and rates of a prevalence
13 of autism, with trends in exposure data. This is
14 ecological what you do.

15 There is a large body of evidence, both for
16 MMR and TCVs, which is not relying on ecological data,
17 where prevalence is not an issue. Epidemic is not an
18 issue. You look at cohort studies. You have children
19 who are exposed to.

20 Q I'm sorry, what studies?

21 A Cohort studies or case control studies, so
22 you know what is the disease status of the child. You
23 know what is his exposure status, and there is a body
24 of data which is replicated across data sets, across
25 countries, showing that exposure of particular

2706A

FOMBONNE - CROSS

1 children to either MMR or TCV vaccines does not
2 increase the risk of autism.

3 This is done in studies where, again, the
4 issue of prevalence, et cetera, is absolutely
5 irrelevant, okay? So this body of data is there, and
6 the ecological studies just confirm what has been
7 found in cohort and case control studies. So I think
8 it's pretty convincing, if you look as I do, at
9 replication of findings a cross studies as my main to
10 learn about the nature.

11 Q The case control studies that you're talking
12 about, the MMR case control studies, were the ones
13 that we've talked about during your testimony today,
14 that didn't include U.S. populations with TCV and MMR
15 exposure. So there aren't any case control studies on
16 that issue, which is the issue here. Am I correct? I
17 mean, we've already talked about. I think we have.

18 A No, I think actually there is more data on
19 this issue than maybe we have discussed. Actually,
20 when I was reviewing my slides at the lunch break --
21 and if I can maybe show you the slide I used this
22 morning. If it's correct, it's the slide of Madsen,
23 for instance.

24 MR. POWERS: So just a quick thing, are we
25 now introducing new thing?

2707A

FOMBONNE - CROSS

1 SPECIAL MASTER HASTINGS: He wants to look
2 at his same slide.

3 MR. POWERS: Oh, same slide, I'm sorry.

4 THE WITNESS: Same slide, yes -- so from
5 this morning?

6 SPECIAL MASTER HASTINGS: Is that the right
7 slide?

8 THE WITNESS: Yes, this is the right slide.

9 SPECIAL MASTER HASTINGS: It's Slide 47.

10 THE WITNESS: Slide 47 -- as we discussed,
11 this study by Hviid, which I presented this morning,
12 shows on the bottom the actual amount of thimerosal
13 which is contained in the vaccines in Denmark. I
14 think you mentioned, at one point, that it was 75
15 micrograms of ethyl mercury which, in fact, it is 125
16 micrograms of ethyl mercury, which was contained in
17 Danish vaccines.

18 So that is important, because when we
19 discuss the Madsen et al. Table 2 findings, where we
20 had data on the joint exposure to MMR and thimerosal
21 continental vaccine, there was a line in 1991 and 1992
22 where, in fact, children were exposed to that level of
23 ethyl mercury and MMR, and that showed no increased
24 incidence, as we discussed this morning. Incidentally,
25 this level of exposure is quite comparable to what

2708A

FOMBONNE - CROSS

1 Michelle Cedillo received. That's one thing.

2 The second thing I would like to show is
3 that, again, the slide I used this morning, which
4 Slide Number 50, and I know we just reviewed it --

5 Q That was your Montreal study.

6 A Yes, you will recall that the slide doesn't
7 show the uptake rate of MMR during that study. But
8 the rate of uptake was quite high. Probably during
9 the periods like 1992, 1993, 1994, 1995, it was
10 somewhere between 93 to 94 percent of MMR uptake.
11 Again, in this population, in particular, the uptake
12 is likely to be 100 percent.

13 So during that particular segment of this
14 ecological study, you have high exposure to ethyl
15 mercury, 200 micrograms, and exposure to MMR, okay?
16 Yet, when it's constant, you see the rates are
17 climbing up.

18 Q For case control studies in the United
19 States looking at thimerosal-containing vaccines,
20 those are the ones we are awaiting from the CDC,
21 correct? We talked about those a minute ago.

22 A I'm sorry, could you repeat?

23 Q On case control studies, looking strictly at
24 thimerosal-containing vaccines, apart from the MMR, in
25 the U.S., we just talked about the CDC ones. But

2709A

FOMBONNE - CROSS

1 those are the only two that are in the works, as far
2 as you know. Is that correct; or do you know of
3 others? I don't want to foreclose that.

4 A There are a number of investigators who are
5 currently collecting data, like large case control
6 studies and population-based samples, where they
7 collected a lot of data, but on environmental factors.
8 Also, everybody collects immunization records. Many
9 people have that. So there will be some data
10 available. But I don't know of any study which prime
11 goal is to investigate that, besides the CDC study.

12 Q I was puzzling over Slide 47. When it was
13 up there, it wasn't making sense to me. Now I see why
14 it might not. Let's get back to Slide 47, if we
15 could. We're looking at these doses: one dose, 25
16 micrograms; two doses, 75 micrograms. I mean, my
17 understanding is that each dose had 25 micrograms.

18 A No, it's 50 micrograms at five weeks; 100
19 micrograms at nine weeks; and 100 micrograms at 10
20 months. This is the amount of thimerosal. The total
21 is therefore 250 for thimerosal, which translates into
22 125 micrograms of ethyl mercury, an exposure which is
23 that of Michelle Cedillo.

24 Q So for each successive dose, they use more
25 thimerosal than the successive -- it just still

2710A

FOMBONNE - CROSS

1 doesn't add up. If it's 25 micrograms of ethyl
2 mercury per dose --

3 A No, it's half of the content of thimerosal,
4 okay, and you have three doses; one who has 50
5 micrograms of thimerosal, then 100 micrograms of
6 thimerosal, and then again 100 micrograms. So that is
7 25 plus 50 plus 50 of ethyl mercury.

8 Q And you're sure that's what the actual
9 content is on the vaccine?

10 A I actually looked because I was surprised
11 that they let that go. But I looked at the Madsen
12 study and the MMR of the Hviid study. Actually, it
13 was written like that, too. It's not a mistake.

14 Q Now a few more things just to I think get us
15 to a point where we can wrap up here. Are you
16 familiar with any population studies that look at
17 industrial emissions as potentially associated with
18 adverse neurological outcomes?

19 A You mean currently or published studies?

20 Q That have been published in say the last say
21 couple of years. And again, not a trick question. I
22 just want to know. I think one was in Texas, the
23 Palmer study, and there was another one, Windham I
24 think was the lead author's name in the Bay area. Are
25 you familiar with those studies?

2711A

FOMBONNE - CROSS

1 A Yes, I recall the Palmer study, yes.

2 Q And the hypothesis in those studies and what
3 those studies found was that in areas where you have
4 high exposures due to industrial emissions including
5 elemental mercury at least, there were initial
6 findings of a higher rate of neurological disorders in
7 those children as compared to people outside the
8 exposure area. Is that a fair statement?

9 A Yes. There was some correlation between
10 autism rates assessed through special educational
11 ascertainment and indices of mercury in the
12 atmosphere. But can I say something about that? But
13 what they did, they collected data on children with
14 autism in I think it's 2001, the study. Let's say
15 that. They collect data on children who were recorded
16 in the special educational system with an autism
17 category in 2001 so they are aged six to 11 say.

18 Then they correlate that with a rate of
19 mercury in 2001. It makes no sense because you don't
20 correlate the rate of mercury in 2001 to explain a
21 disorder which occurred four, five, six years ago.
22 The specification of the disease model is completely
23 wrong in that study, and that showed that their
24 statistics are spurious.

25 Q So your opinion would be that those studies

FOMBONNE - CROSS

1 are uninformative?

2 A No. No, I think it could be informative,
3 but that particular study is completely not well
4 designed for the reason I just indicated. Unless they
5 look at reverse causation.

6 Q Given what I understand from your testimony,
7 that prevalence rates in the U.S. population are
8 roughly the same today as they were say 20 years ago,
9 is that fair? Actually, I should correct that. I
10 used the wrong word.

11 The actual incidence of autism in the United
12 States, that is the percentage of people in the
13 population who are autistic, is relatively the same
14 now as it was say 20 years ago. Correct?

15 A We can assume that.

16 Q I'm not asking about prevalence rates and
17 inflation, but just the actual, what you believe to be
18 the real incident rate has basically been static over
19 the last 20 years.

20 A Yes, a starting assumption, yes.

21 Q Assuming that, and I didn't even attempt to
22 work up the numbers, and I just don't know whether you
23 have but I'm curious. Based on that analysis, how
24 many autistic adults, that is say over the age of 18,
25 how many autistic adults should we be seeing in the

FOMBONNE - CROSS

1 U.S. population? Do you have an estimate?

2 A In numbers? I don't know. I have not made
3 a calculation, but it's easy to do if you want. You
4 need to account for the fact that there might be some
5 increase in mortality rates when the studies show that
6 the standardized mortality ratio in autism is
7 increased, so there is more mortality than the other
8 groups so you have to account for a few things of that
9 kind.

10 Q And again, I was just trying to get an idea
11 if you had a number, because I'm curious as to how
12 many autistic adults we ought to be encountering in
13 the U.S. population if the true incidences remain the
14 same historically. You don't have that number, but
15 you think it can be calculated I assume just by using
16 the 60 out of 10,000 and mortality within that.

17 A Well, yes. Probably with an attenuation
18 factor of that kind, so I don't know which kind of
19 rate I would apply, but yes, you could do these
20 calculations.

21 The calculations that we provide are based
22 on empirical studies. The point in terms of adults is
23 that there has been no survey of autism spectrum
24 conditions in the adult population. That's something
25 which remains to be done. Unless it is done,

2714A

FOMBONNE - CROSS

1 speculations will go wildly, you know?

2 Q Right. In any direction. I mean, if you
3 don't know, people can speculate and hypothesize and
4 make all sorts of assumptions without facts, correct?

5 A Of course. Yes.

6 Q Just very quickly here, you've testified as
7 an epidemiologist today. We've talked about some
8 underlying causation issues. But so much of what
9 you've been talking about is related to diagnoses. I
10 was curious how many autistic children you actually
11 treat as a physician.

12 A Currently you mean?

13 Q Yes, a ballpark number.

14 A My caseload is probably like 200, 250 a
15 year. I don't know. I have ongoing patients who come
16 back from follow-up. I assess probably these days
17 about 150 new cases a year, maybe a bit more than
18 that. I see kids for psychopharmacology clinics, I
19 see a number of them which come back regularly for
20 treatment and management.

21 Q And for the 150 children that you assess
22 each year, again without burning a huge amount of
23 time, can you just give me a quick description of how
24 you assess them? If you could just run through a list
25 of how you would assess those 150 children that you

FOMBONNE - CROSS

1 see?

2 A It really varies. We use, the standard
3 technique that we use usually is to use an autism
4 diagnostic interview which is a developmental
5 interview with the parents. That lasts three hours.
6 We then have the child coming back with his parents.
7 We do then a neurological examination. We do in
8 different days a speech and language assessment, a
9 cognitive assessment, occupational therapy assessment.
10 We do the regular medical exam, family history and
11 everything. I usually do an ADOS with the children
12 which is a direct examination. So that's the full,
13 complete assessment.

14 The one we use for cases which are more
15 complex, that would be typically children who have
16 some language skills, which are not mentally retarded,
17 or children who are included in research studies where
18 we want to do the full phenotypic assessment.

19 On the other hand, because of pressure on
20 our time and on our waiting list, I do sometimes see
21 children within about two hours. When the case is not
22 complex I can do a relatively good job of assessing a
23 new child, completing my diagnostic evaluation in that
24 timeframe, but I always see the child again, have a
25 follow-up. So that varies. It will be sometimes more

2716A

FOMBONNE - CROSS

1 incomplete.

2 And as I said this morning, sometimes you
3 walk into the room and you see the child and you know
4 he's autistic, yet you have to spend time to do the --

5 Q Sure. And then among the patients that you
6 have where you've diagnosed them as autistic, do you
7 have a sense of how many of those children have
8 gastrointestinal problems or symptoms?

9 A I can give you a range. Suprisingly I asked
10 the question about that because it has been on the
11 agenda so now we ask questions about gastrointestinal
12 symptoms, diarrhea, constipation.

13 I would think in my clinical load, it's
14 about 10-15 percent, 20 percent at most that are
15 reporting, many of them are functional symptoms which
16 are not worrying parents and they disappear very
17 quickly.

18 In our network we divide the medical clinic
19 so we have a pediatrician who is there to investigate
20 medical difficulties in the children. We can then
21 refer to them if there is concern about diarrhea,
22 constipation, diet, sleep or whatever. I refer to
23 her, but very infrequently.

24 Q Do you have any idea of what sort of
25 treatments they use for those children that you refer?

2716B

FOMBONNE - CROSS

1 A One thing that they do, they investigate the

2717A

FOMBONNE - CROSS

1 diet of these children because it's very important to
2 recognize that many of them have poor diet due to
3 their behavioral restrictions, so they eat nonfiber
4 food and other things which can lead to constipation
5 and then overflow diarrhea. So dieting advice is an
6 important aspect of the management.

7 Also some of them do have pica. They eat
8 nonedible food, and that can create some GI problems.
9 But again, it's not a huge proportion of the children
10 I see, and these are children between age 18 months to
11 five and six.

12 Q Do you recommend any particular diets for
13 the autistic children you have? We heard a little bit
14 of testimony here or references to things like the
15 gluten-free, casein-free diet. Is that something that
16 you recommend in your care and treatment of autistic
17 children?

18 A No. We do not recommend, there is no
19 evidence-based study which would suggest that it's
20 useful. There are ongoing studies to look at RCTs
21 which are examining this question in Rochester, New
22 York in particular. But so far it's not something
23 that we advise to do routinely.

24 Q Do you do testing for urinary porphyrins for
25 autistic children in your clinic?

FOMBONNE - CROSS

1 A No. Usually not. Not in the standard
2 child. Sometimes we have children where there are
3 unusual dysmorphic signs so we refer them to medical
4 genetic consultation, and then they do the full array
5 of metabolic testing including this one.

6 MR. MATANOSKI: Mr. Powers, I think you're
7 getting close to the end, but is there going to be a
8 question about his Direct testimony coming up?

9 MR. POWERS: Yes, there are all questions
10 that relate to what he does in his diagnosis.

11 MR. MATANOSKI: And how are they related to
12 his Direct testimony?

13 MR. POWERS: Rather than asking me what I'm
14 doing, I mean --

15 SPECIAL MASTER HASTINGS: He's making the
16 point that most of these questions don't seem to be
17 related to the epidemiologic --

18 MR. POWERS: But they're related to some of
19 the causation factors. He talked in his presentation
20 about, and certainly in the papers that were submitted
21 today, the things I was just talking about. Gut
22 symptoms, bowel symptoms, symptomology, when they
23 appear, how far away they appear from a vaccination. I
24 was just trying to spend a few minutes to explore
25 those issues simply to see if there's anything he can

FOMBONNE - CROSS

1 say about what he does in his diagnostic program that
2 would inform the causation opinions he was talking
3 about.

4 SPECIAL MASTER HASTINGS: I remember him
5 talking about epidemiologic stuff this morning, but
6 I'm going to give you some leeway on --

7 MR. POWERS: There truly is like a couple of
8 minutes.

9 SPECIAL MASTER HASTINGS: All right. Go for
10 it.

11 MR. POWERS: And it --

12 SPECIAL MASTER HASTINGS: Go ahead.

13 MR. POWERS: That might have been it.

14 (Laughter.)

15 MR. POWERS: That was it actually on
16 diagnoses and clinical management. Then just a
17 question, and I don't know if you know this.

18 BY MR. POWERS:

19 Q As you understand, I'm sure there will be
20 additional test cases that are going to be heard here.
21 Do you plan on coming back to testify and offer Direct
22 testimony in cases, particularly on cases with the
23 theory that Thimerosal-containing vaccines independent
24 of the MMR are implicated in autism spectrum
25 disorders?

FOMBONNE - CROSS

1 MR. MATANOSKI: Actually, that's a question
2 that goes to our approach here in terms of the
3 attorneys. I don't think he's qualified to answer it.
4 Whether I decide or the Department of Justice or
5 Health and Human Services decides, what they decide to
6 do in the upcoming cases is a matter of our trial
7 strategy.

8 MR. POWERS: But he, and you're not his
9 attorney, and I'm asking this witness whether he is
10 planning --

11 MR. MATANOSKI: Whether he appears or not is
12 going to be a decision made by the Department of
13 Justice and Health and Human Services, not by the
14 witness.

15 THE WITNESS: I am planning to go back to
16 Montreal tonight because I have a clinic tomorrow
17 morning, and that's what I want.

18 BY MR. POWERS:

19 Q So you don't want to sit around in the room
20 and listen to additional testimony from other
21 witnesses any more?

22 A No, it's enough.

23 Q And about how many hours of time did you
24 spend sitting in the room listening to witnesses in
25 this case?

FOMBONNE - CROSS

1 A I don't know. You've seen me.

2 Q A ballpark?

3 A Maybe five days.

4 Q And during the time that you were listening
5 to other witnesses when you were not testifying, were
6 you getting paid for the time that you were here?

7 A I don't know yet.

8 (Laughter.)

9 Q There are a lot of people who don't know if
10 they're being paid for their time.

11 A I hope I will.

12 Q I think that would be the expectation from
13 your end, I'm not surprised.

14 Have you submitted any sort of bills or
15 invoices to the Department of Justice for your work in
16 this case so far?

17 A Yes, I think one or two.

18 Q Do you have an idea of how much money you
19 have billed so far to the Department of Justice in
20 this case?

21 A No. I've received nothing.

22 Q In terms of that you've billed with an
23 expectation. Do you have even a ballpark number?

24 A No, because I don't have it in front of me
25 so I don't know.

FOMBONNE - CROSS

1 Q How about payment in other cases in which
2 you've testified? I know the Jordan Easter case in
3 Texas, you gave a report, you did a deposition, you
4 testified at a Daubert hearing. Do you know what you
5 ultimately billed the Defendants in that case?

6 A I spent like three days in Marshall, Texas.

7 Q Which is a beautiful place to spend three
8 days. I was actually there the day that you testified
9 --

10 A Oh, really. So yes, I recall that stay in
11 Texas. No, I don't recall, I don't have any precise
12 figure. I think last week I mentioned that \$60,000 or
13 \$70,000 was probably an accurate estimate.

14 Q And then in other civil cases where you've
15 testified, do you have a cumulative number? I really
16 don't want to spend a huge amount of time on the
17 issue, but really what I'd like to know is, for the
18 entire time that you've been involved in litigation
19 related to Thimerosal or MMR being associated with
20 autism, anything related to those cases, do you have
21 an idea of how much money you've been paid or expect
22 to be paid? An aggregate number?

23 A No, I really put everything in a shoe box
24 and go to the tax man at the end of the day, so I
25 don't know. I don't know. I probably spend on

FOMBONNE - CROSS

1 average 10 to 15 hours a month, on average.

2 Q And in the civil cases billing what? \$500
3 an hour?

4 A Yes.

5 Q And in the DOJ, in the cases in this
6 program, \$250 an hour?

7 A That's my understanding.

8 MR. POWERS: I have nothing else for this
9 witness. Thank you.

10 MR. MATANOSKI: All right. Tom, you were
11 going to clear up one matter from --

12 MR. POWERS: When we're completely done. I
13 don't know if you have Redirect.

14 SPECIAL MASTER HASTINGS: Any Redirect for
15 this witness?

16 MS. RICCIARDELLA: We do. Can we take a
17 five minute recess?

18 SPECIAL MASTER HASTINGS: Okay. Let's take
19 our afternoon break at this time. Let's take a 10-
20 minute break.

21 MS. RICCIARDELLA: Thank you.

22 (Whereupon, a short recess was taken.)

23 SPECIAL MASTER HASTINGS: We're back from
24 our afternoon break. Dr. Fombonne is still on the
25 witness stand and now we'll have some Redirect

FOMBONNE - REDIRECT

1 Examination by Ms. Ricciardella for the Respondent.

2 MS. RICCIARDELLA: Thank you, Special
3 Master.

4 REDIRECT EXAMINATION

5 BY MS. RICCIARDELLA:

6 Q Just a few questions, Mr. Fombonne. I have
7 to speak up because I'm getting the same "battery low"
8 message that Mr. Powers got.

9 You were asked at the very start of your
10 Cross-Examination about different phenotypes, what
11 different characteristics can classify as a phenotype
12 of autism. But you and others have studied the
13 particular phenotype that is at issue in this
14 litigation, namely autistic enterocolitis, is that
15 correct?

16 A Yes.

17 Q What have those studies shown about this
18 particular so-called phenotype of autistic
19 enterocolitis?

20 A The studies by and large show there is no
21 validity to this particular phenotype as a separate
22 entity. So the notion that it would be regression
23 occurring days after the vaccination in a child with
24 previously absolutely normal and will regress with GI
25 symptoms is not supported by most data which has

2725A

FOMBONNE - REDIRECT

1 looked at this question so there is no evidence of
2 increased rates of regressive autism after MMR is
3 introduced or it doesn't decrease when it's removed,
4 the association with GI symptoms is ambiguous. There
5 is no evidence that GI symptoms have increased in
6 autism over time. And there is certainly no evidence
7 that the regression occurs more than in non-regressive
8 cases just after the MMR vaccination. So that's very
9 clear from the range of studies which have replicated
10 these findings.

11 Q Now there was also discussion, Mr. Powers
12 asked you about congenital rubella and Thalidomide.
13 Now those exposures, of the children who had exposure
14 to congenital rubella and Thalidomide who later
15 developed autism, are those exposures prenatal or
16 postnatal?

17 A No, these are prenatal exposures. They are
18 part of a small set of environmental prenatal exposure
19 which has been documented to increase the risk of
20 autism. So a few medications like misoprostol and
21 others, valproic acid, Thalidomide, maybe terbutalene
22 and other kinds of events occurring during pregnancy
23 are known to increase the risk of autism in some
24 fetuses. But there is not much evidence of postnatal
25 environmental influences. There

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FOMBONNE - REDIRECT

1 are a few maybe case reports which raise the
2 possibility, but what we know about environmental
3 factors so far is entirely confined to the pregnancy
4 or the post-conception weeks. That's very clear.

5 Q You were also asked about different
6 diagnostic criteria that make up the DSM-IV and the
7 ICD-10. If I take a child, the same child, and I have
8 one clinician applying the DSM-IV criteria and another
9 clinician applying the ICD-10, are the two clinicians
10 going to come up with the same diagnosis of the same
11 child?

12 A Yes, absolutely.

13 Q And the studies that use either the ICD-10
14 or the DSM-IV criteria, there's no mixing and matching
15 of criteria within a study, correct? The
16 investigators use a consistent criterion, either the
17 DSM-IV or the ICD-10, in each study.

18 A I think what matters, within a study people
19 would tend to stick to one particular set of
20 diagnostic criteria, and within that framework you can
21 therefore assess association with exposure or trends
22 over time, provided that you don't shift diagnostic
23 systems as you go along.

24 But having said that, ICD-10 definition of
25 autistic disorder is closely comparable to DSM-IV and

FOMBONNE - REDIRECT

1 there is no differences of views or algorithms when we
2 use ICD-10 in European countries or DSM-IV in North
3 American countries. It's pretty much the same. There
4 are a few differences regarding PDD-NOS, but they can
5 be made up to be comparable.

6 Q Doctor, Mr. Powers showed you a 27 page
7 review article by Craig Newschaffer which you hadn't
8 read, and of the 27 pages he asked you to comment on
9 one sentence, actually half of a sentence found on
10 page 239. What he didn't ask you to comment on was
11 the second clause of that sentence that states,
12 "...because it is very difficult to develop
13 quantifiable estimates of diagnostic effects and
14 virtually impossible to prove or disprove temporal
15 changes in autism population risk profiles given the
16 condition's unknown etiology."

17 Do you have any comment on that phrase and
18 the entire paragraph that Mr. Powers asked you to
19 comment on?

20 A I disagree with that second part of this
21 paragraph. It says because the disorder is of unknown
22 etiology you cannot assess temporal change in the rate
23 of this condition which is absolutely, it's an ill-
24 informed statement in medicine. People have looked at
25 trends over time, recorded the incidence of disorder

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FOMBONNE - REDIRECT

1 of various disorders without knowing the etiology.
2 It's actually a mean to progress in the understanding
3 of the etiology of a disorder to collect
4 epidemiological data, time trends, to compare rates
5 across nations, across areas. It can be done provided
6 that you have a reliable definition of what you study,
7 even if you don't know the etiology.

8 So I really disagree with this part of the
9 statement which I think is not well informed.

10 Q Doctor, you were also asked about slide 7 of
11 your presentation today. It was a Finland study.
12 That study done out of Finland, that study wasn't
13 designed to test what the prevalence rates of autistic
14 spectrum disorders were at that point in time,
15 correct?

16 A No. The point of that slide is not to look
17 at prevalence or whether or not it's accurate or not.
18 Whatever is the prevalence in that study doesn't
19 matter to the demonstration which showed that on the
20 same data set, the same children, same study, if you
21 apply different criteria the old criteria give low
22 rates; the more recent criteria give three-fold
23 higher. That is what is the take-home message of that
24 study.

25 Q Doctor, you were asked a question about your

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FOMBONNE - REDIRECT

1 2006 Montreal study. There was some confusion about

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FOMBONNE - REDIRECT

1 the term population, if it truly meant population as
2 lay people mean it or a sample. You answered a
3 question about uptake in prevalence and I think there
4 might be some confusion.

5 In your Montreal study, why did you not use
6 prevalence data for the same sample that you had
7 chosen because of the vaccine uptake?

8 A We often prevalence data from a sample which
9 is representative of a given population in a given
10 area. Then the next question was to obtain some kind
11 of estimate about trends in vaccine uptakes to compare
12 it to the trends in the prevalence that we had.

13 Had we had data about vaccine uptake rates
14 in the same geographical area from where we did our
15 study, that would have been the best approach, but we
16 didn't have such data. The next thing that we could
17 go for would be to look at a few isolated studies in
18 Montreal which were done with different samples,
19 different methods over that study, so they would even
20 not be comparable from survey to survey. So assessing
21 the trends in that condition would be very difficult.

22 In addition, the whole island of Montreal is
23 very disparate in terms of there are some regions,
24 some areas big, and so there are wealthy areas,
25 impoverished areas, and depending on where you do your

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FOMBONNE - REDIRECT

1 survey to evaluate vaccine uptake would affect your
2 results.

3 So to compare to a particular privileged
4 area, Montreal was not offering data that you could
5 use. The only data we could really use was the Quebec
6 City regular surveys in a sort of an area where the
7 population is wealthy, there is not much of
8 unemployment rate, and the survey were conducted most
9 years with the same methods, and that allowed us to
10 estimate the vaccine uptake for MMR over time and get
11 this trend that we want to obtain. The rates of a
12 different population is less than optimal, but it's
13 the best that we could do. That would be done in most
14 ecological studies.

15 Q To stay on the topic of ecological studies,
16 Mr. Powers was discussing ecological studies and
17 suggesting that your reasoning wasn't taking into
18 account changes in case ascertainment, changes in
19 diagnostic criteria, et cetera. Now in ecological
20 studies, though, do trends on prevalence rates of
21 autism change when you add MMR vaccines or Thimerosal-
22 containing vaccines into the, when they're introduced
23 or discontinued in the population?

24 A No. The idea is that if we, changing
25 diagnostic criteria or certain ascertainment can

FOMBONNE - REDIRECT

1 affect the results when you want to estimate the
2 magnitude of a condition in a given population. so
3 that would affect the point prevalence rate at a given
4 point in time. Now when people generate trends, what
5 you want to have is the trends are evaluated with
6 methods which are more or less constant, so there is
7 no major change in diagnostic content, or a major
8 change in diagnostic criteria, or there is no suddenly
9 a new ascertainment which is made in a population.

10 So provided that you have your methods of
11 counting the cases which are uniform over time, then
12 you can assess a trend.

13 Your methods could be not optimal. You
14 could, for instance, in assessing trends in the rates
15 of autism, only identify 70 percent of the cases in a
16 population. And if you identify 70 percent of the
17 cases in the population constantly over time then your
18 trend will be actually an accurate trend even though
19 the level of the rate is not accurate. The trend will
20 be accurate.

21 So under such circumstances if you have a
22 trend which is well estimated, then you can really
23 look at the effect of vaccination policies and
24 traditional new vaccines, removing that vaccination,
25 and see if it affects the trend. That's what you do.

FOMBONNE - REDIRECT

1 It has been done in various studies I quoted this
2 morning.

3 Q One more question.

4 Doctor, there was some discussion towards
5 the end of your Cross about different ways that you
6 diagnose a child with autism. Although to assess
7 early signs and symptoms of autism, can you use home
8 videos as a tool to look at what are potential early
9 signs and symptoms of the autism in that child?

10 A Yes, we do that in our clinics these days.
11 we have often parents who come with videos or DVDs
12 because they have observed unusual behaviors in their
13 children that we are unlikely to observe in our
14 clinics. When there are some unusual repetitive
15 movements, for instance, we sometimes don't see in our
16 clinic during the time of the assessment. It's a new
17 place, the child doesn't really behave in the way he
18 behaves across time, across context, the way the
19 parents see him. So videos in that respect are often
20 used by parents to document a behavior which they see
21 that we will not see. So they provide this as
22 evidence that we use. We use, we incorporate that
23 evidence in our diagnostic assessment.

24 The home videos have been particularly
25 useful to look at early signs of autism, predictors of

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FOMBONNE - REDIRECT

1 later autism diagnosis. The studies we reviewed last
2 week have been extremely influential in trying to
3 pinpoint particular communication and social
4 abnormalities which can be seen at age 10 and 12
5 months in young babies which have subsequently been
6 diagnosed with autism, even though parents do not
7 recognize at the time of the abnormalities that they
8 are abnormal behaviors. But the studies are really
9 unambiguous in their findings by using these videos,
10 looking at early signs of autism. You can predict a
11 later autism diagnosis with a high level of accuracy.

12 Q One final question.

13 You were asked a series of questions about
14 the Verstraeten study, using the Vaccine Safety
15 Datalink. Doctor, did you look at Petitioner's
16 Exhibit 91 from the Autism Omnibus proceeding which is
17 the reanalysis done by the PSC's own experts, Doctors
18 Uatin and Lalley?

19 A Yes.

20 Q Do they not state, and I quote, "We
21 generally believe that the methodology employed by the
22 CDC investigators was sound and that their findings
23 are valid. Do you recall that statement?"

24 A Yes, I read the reanalysis and this is their
25 conclusion.

FOMBONNE - REDIRECT

1 MS. RICCIARDELLA: I have no further
2 questions.

3 SPECIAL MASTER HASTINGS: From Petitioners,
4 any further questions of this witness?

5 MR. POWERS: Just a couple. Literally a
6 couple. The questions are quick, I anticipate the
7 answers will be quick, too.

8 BY MR. POWERS:

9 Q Dr. Fombonne, you mentioned when I was
10 asking you questions earlier that your rate of
11 gastrointestinal symptoms was about 10 to 20 percent
12 in your autistic children. Do you remember that?

13 A No, you asked me to guesstimate in my
14 clinic. You should know that in my clinic hospital
15 children are referred to our program as opposed to
16 going to neurology, for instance, because they have
17 different degrees of mental retardation. So it's
18 based on my particular program which has a high number
19 of children, so that's what it is.

20 Q Then in 2006 you were the co-author on a
21 paper with D'Souza and Dr. Ward who testified earlier.
22 Do you recall that paper?

23 And in that paper on page 1669,
24 gastrointestinal symptoms were reported in almost 80
25 percent of children from the autistic group. Do you

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FOMBONNE - REDIRECT

1 recall that?

2 A Yes. I think we probably have chosen the
3 children for this particular reason because we were
4 looking again at the autistic enterocolitis phenotype.

5 Q Okay. The number jumped out at me and I
6 just wanted to --

7 A Yes, but just to elaborate just one minute
8 on that.

9 Q Okay. And I'm listening, but I dropped
10 something, so I'm picking it up.

11 A All right. The way gastrointestinal
12 symptoms is assessed in various studies is highly
13 variable. People sometimes ask the question, has your
14 child ever had diarrhea and constipation? If you ask
15 this question in this room the rate will be 100
16 percent, you know? Then people sometimes do three
17 months in a row. So the way the question is asked can
18 really influence the actual rate.

19 If you look at studies where GI symptoms
20 rate have been published, there is a complete lack of
21 standardization in how you define, how you measure GI
22 symptoms. But pediatricians report, by medical
23 records, by parental reports, how far did you go back?
24 Did you impose a duration criterion for the symptoms
25 to be counted? It's very, not complicated, but it's

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FOMBONNE - REDIRECT

1 very haphazard across studies. Hence we have rates
2 which vary enormously.

3 Q You mentioned also earlier that you had a
4 six year old patient with pubic hair. Was that a
5 precocious puberty case?

6 A Yes.

7 Q Do you see that often in your practice?
8 Precocious puberty?

9 A No. It was one case.

10 Q Again, just curious.

11 Finally, in the materials you talked about
12 the autism epidemic. Have you heard any allegation in
13 Petitioner's case in chief that relies on the
14 existence of an autism epidemic of proof of causation
15 in the Cedillo case?

16 A In the Petitioner's documentation? Many
17 studies have been referenced, that make that claim.

18 Q I'm just talking about the case that was put
19 on, have you heard any allegation that the finding of
20 an epidemic of autism is part of the proof that
21 Petitioners are relying on here in the Cedillo case?

22 MR. MATANOSKI: Actually, Tom, there was
23 Cross on that that presented that as a postulate. Not
24 of this witness.

25 THE WITNESS: My understanding is that

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FOMBONNE - REDIRECT

1 Wakefield hypothesis is significant in that particular
2 case, and it was one of his claims. So his theory is
3 tied up to this idea.

4 BY MR. POWERS:

5 Q So it was from Wakefield that you see it,
6 correct?

7 A I think so, yes.

8 MR. POWERS: Nothing else. Thanks.

9 SPECIAL MASTER HASTINGS: Anything further
10 for this witness?

11 MR. MATANOSKI: No sir.

12 (Witness excused.)

13 SPECIAL MASTER HASTINGS: Should we start
14 with the testimony of Dr. Griffin?

15 MR. MATANOSKI: Yes, sir.

16 SPECIAL MASTER HASTINGS: Dr. Griffin,
17 please take the witness stand.

18 MR. POWERS: One thing, just for the record.
19 In my Cross-Examination of Dr. Wiznitzer we discussed
20 the possibility that he might have testified as an
21 expert witness for the defense in the case of Jordan
22 Easter. I found that was simply a miscommunication
23 with the Plaintiff's counsel. Dr. Wiznitzer did not
24 testify or appear as an expert witness in Easter and I
25 didn't want to leave the impression that he had and

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1 was being disingenuous. As a matter of fact, he has
2 not.

3 SPECIAL MASTER HASTINGS: Thank you for
4 clearing that up, sir.

5 All right. We have Dr. Griffin at the
6 witness table, and Dr. Griffin, I'm going to ask you
7 if you'd raise your right hand for me.

8 Whereupon,

9 DIANE GRIFFIN

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

12 SPECIAL MASTER HASTINGS: Please go ahead
13 then, Mr. Matanoski.

14 MR. MATANOSKI: Thank you, Your Honor. I'm
15 hoping that we keep this brief. We don't have a whole
16 lot of slides, and I'm not real familiar with using
17 them. I'm going to try to tell you which slide we're
18 on.

19 SPECIAL MASTER HASTINGS: All right.

20 MR. MATANOSKI: I may forget. I may be like
21 the person at the light and the light goes green and
22 you're waiting for them to pick up on it. If you give
23 me a moment, I may pick up on it. If not, give me a
24 little toot on the horn to let me know that I've
25 forgotten to say which slide we're on.

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GRIFFIN - DIRECT

1 SPECIAL MASTER HASTINGS: All right. Do we
2 have a handout you're going to give us?

3 MR. MATANOSKI: Actually Mr. Rooney will be
4 giving out a handout right now.

5 MR. Matanoski: May I approach the bench?

6 SPECIAL MASTER HASTINGS: Yes, please.

7 (Pause.)

8 SPECIAL MASTER HASTINGS: All right. Let's
9 mark this as Respondent's, I think we're up to 22, so
10 this will be 23.

11 DIRECT EXAMINATION

12 BY MR. MATANOSKI:

13 Q Good afternoon, Dr. Griffin.

14 A Good afternoon.

15 Q Could you start with telling us a little bit
16 about your schooling? We could start with where you
17 want to college.

18 A I went to college at Augustana College in
19 Rock Island, Illinois, where I got a BA degree in
20 Biology.

21 Q From there where did you go?

22 A From there I went to Stanford University
23 Medical School where I got an MD and a PhD. the PhD
24 was in immunology where I was studying
25 immunoglobulins.

GRIFFIN - DIRECT

1 Q After that, what path did your career take?

2 A My path went to Johns Hopkins where I've
3 been ever since, so I have an easy CV. I did a post-
4 doctoral fellowship with Richard Johnson who is a
5 neurovirologist and we went to Hopkins because my
6 husband was a neurology resident. And after a post-
7 doctoral fellowship with Dr. Johnson, then I joined
8 the faculty in the Department of Medicine and
9 Neurology. I've always had a joint appointment in
10 those two departments. Where I progressed through the
11 ranks to Professor. Then in 1994 I became Chair of
12 the Department of Molecular Microbiology and
13 Immunology in the Johns Hopkins Bloomberg School of
14 Public Health. So I moved across the street, but I
15 retained my appointments in the School of Medicine.

16 Q Doctor, first of all could you try to speak
17 a little slower?

18 A Okay.

19 Q Right now, this late in the day, my mind is
20 working very slowly. If you could try to speak a
21 little slower, that would be great.

22 How long have you been at Hopkins?

23 A I went to Hopkins in 1970 so I have been
24 there ever since. That is 37 years. If my math is
25 correct.

GRIFFIN - DIRECT

1 Q As Chair of the Department of Molecular
2 Biology, I hope I got that right.

3 A Molecular Microbiology and Immunology, but
4 you're not the only one who gets confused.

5 Q What do your duties entail?

6 A I'm Chair of the department so I have a lot
7 of administrative duties with respect to both
8 university affairs, school affairs, departmental
9 affairs, faculty mentoring, faculty recruitment,
10 faculty promotion, all the things that go with running
11 a department, basically, and then in addition, it's
12 sort of a typical academic appointment, I also have my
13 own research program so I have a research program
14 that's in viral pathogenesis, and we'll talk I guess
15 more about that later. But in addition to that, so I
16 spend a substantial amount of time mentoring people
17 within the lab, going over data, writing papers, et
18 cetera, that are related to the research component.

19 Then there's the third component of
20 education that is a more formal education kind of
21 process, teaching the graduate level virology course,
22 lecturing in a number of other courses, teaching
23 medical students microbiology, that sort of thing.

24 Q I don't want to belabor what's on your CV,
25 but if you could just go through some of the

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GRIFFIN - DIRECT

1 professional societies that you belong to that may
2 have application to what you're going to testify here
3 today.

4 A I belong to societies that are relevant to
5 infectious diseases. I'm a fellow of IDSA, the
6 Infectious Disease Society of America. I'm in
7 American Society for Virology, in fact I was President
8 of that organization. I'm a member of the American
9 Association of Immunologists. I am, the other things
10 that are relevant. Well, I'm a fellow of the American
11 Academy of Microbiology. I'm a fellow of the American
12 Association for Advancement of Sciences. Then I'm
13 also a member of the Institute of Medicine and also
14 the National Academy of Sciences.

15 Q With respect to the Association for the
16 Advancement of Sciences, did you hold a special
17 position there?

18 A I was, in fact I'm retiring Chair, past
19 Chair, something like that of the Medical Sciences
20 Division of the AAAS, yes.

21 Q With respect to journals that may have some
22 application to what you're going to testify to here
23 today, are you on the editorial board or an editor of
24 journals in say virology or immunology?

25 A I was an editor for 10 years of the Journal

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GRIFFIN - DIRECT

1 of Virology. I'm on the editorial boards of the
2 Journal of Clinical Investigation of Virology, of the
3 Journal of Neurovirology. I'm an editor of the
4 Proceedings of the National Academy of Sciences.
5 Those are probably the main editorial things I'm doing
6 now.

7 Q When did you begin studying the measles
8 virus?

9 A I started as a post-doc, probably in 1973 or
10 1974 we first started getting interested in measles.
11 So as I mentioned, I went to Johns Hopkins as a post-
12 doctoral fellow in sort of neurovirology and
13 infectious diseases. I combined clinical training at
14 the same time with research training during that
15 period of time.

16 I was studying primarily encephalitis, alpha
17 virus encephalitis. As I mentioned, the laboratory
18 was particularly, it was a neurovirology laboratory.
19 I was interested in virus infections of the nervous
20 system.

21 One of the diseases that has been very
22 puzzling and actually still is very puzzling, is a
23 post-infectious encephalomyelitis that can complicate
24 a number of viral infections, but it particularly
25 complicates measles.

GRIFFIN - DIRECT

1 Dr. Johnson had done a sabbatical, a period
2 of time in Peru where they were seeing actually quite
3 a large number of cases, they had endemic measles at
4 that time, were seeing quite a large number of those
5 cases so we thought that would be an opportunity to
6 try and understand better how that particular
7 complication occurred.

8 Subsequently we understand it as an
9 autoimmune disease that occurs in close association
10 with measles. It's not a progressive disease. It's a
11 rather characteristic disease that occurs primarily in
12 people who get measles when they're older, usually
13 five or ten. In that particular population in Peru
14 there was a lot of in migration, so there were a lot
15 of older people getting measles, sort of an unusual
16 situation.

17 Q What prompted you to study the measles virus
18 in particular?

19 A As I say, we started because we were
20 interested in this neurologic complication and we
21 thought that, as a part of that we were studying those
22 patients that had that particular complication and
23 then comparing them to patients who didn't have that
24 complication. So those were children that either had
25 measles with no complications or had measles with

GRIFFIN - DIRECT

1 other infectious diseases which is the most common
2 complication of measles. So we'd stratify the
3 patients into these three groups basically. Then also
4 patients usually that had other, similar age children
5 that had other infectious diseases as a control group
6 or no disease.

7 Q I can tell from your resume, you continued
8 with studying measles virus. Why did you --

9 A Right. What our initial studies found was
10 that, our original hypothesis was there was going to
11 be something different about the immune response to
12 measles that was occurring in these children that got
13 the neurologic complications versus the ones that
14 didn't, that got other complications.

15 What we found is that they all had this
16 immune suppression that was very profound and that
17 occurred in association with the acute disease, and it
18 really wasn't different between the different
19 complications of measles. It wasn't identifiably
20 different in a way that helped you to try to figure
21 out what the difference was between them. So
22 consequently we got interested in what's measles
23 immunosuppression, what's that biologically, and how
24 can you understand that particular problem. Then
25 subsequently we got interested in other aspects. It's

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1 a fascinating disease biologically, and it's an
2 interesting virus. It just progressed.

3 Currently we're doing a lot of vaccine
4 studies to develop a vaccine that could be used in
5 younger children. Protective immunity. What does a
6 vaccine have to do in order to protect you from
7 getting infected? We continue to study
8 immunosuppression in measles. We could study
9 clearance, what aspect of the immune response is
10 important for clearing the virus? Those are all
11 questions that are ongoing at the moment.

12 Q So you've not only studied measles virus but
13 you've also studied the effects of immunization with
14 measles vaccine?

15 A Absolutely, yes.

16 Q Do you know offhand about how many published
17 articles you have on measles virus or measles virus
18 vaccine or MMR?

19 A I don't know for sure, but I would guess
20 around 100, both peer reviewed primary publications
21 and review articles and chapters and that sort of
22 thing. I would imagine it's in that park.

23 Q I know this is covered a bit in your CV, but
24 the book, "Fields Virology", what is that book?

25 A Well, it's sort of what most of us consider

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1 the bible for virologists. It's a big, fat, two-
2 volume book that you go to that's in its fifth
3 edition, that you go to when you want to look up
4 anything you want to know about those particular
5 viruses. It's too fat for a textbook. It's a
6 reference book. It really is a reference book for
7 virologists.

8 Q Did you contribute to that book?

9 A I'm an editor on that book and also I've
10 written two of the chapters, one on alpha viruses and
11 the other on measles virus.

12 Q How long have you been contributing a
13 chapter on measles virus to --

14 A I think I've done the measles chapter the
15 last three editions, so the third, fourth and fifth
16 edition. They come out about every four years or so.

17 Q Do you write any other book chapters with
18 respect to measles virus?

19 A I write and review book chapters regularly.
20 Well, I'm trying to avoid it because they're really
21 time consuming. For a number of different other
22 books, compendia of articles, et cetera. I'm editing
23 one right now, actually, for current topics in
24 microbiology and immunology on measles. Michael
25 Oldstone and I are editing that.

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1 Q I'm sorry, with whom?

2 A Michael Oldstone. He's a virologist in --
3 He also works on measles at the Script institute, so
4 the two of us are putting together, we're editing
5 currently a book on measles. It's sort of an
6 anniversary of the vaccine.

7 Q I'm going to ask you some questions about
8 whether you've been in the courtroom before and any
9 contacts you may have had with litigation before.

10 You're doing fine so far on the witness
11 chair. This isn't why I'm asking you that.

12 Have you ever testified before?

13 A I've only testified once before, which was
14 in a malpractice case before, it was a board in
15 Maryland that hears, it's not actually a courtroom
16 trial, it's maybe sort of like this. There's a person
17 or two or three that hears a case before it,
18 adjudicates, basically, malpractice cases. I disliked
19 the experience greatly, and have avoided it ever since
20 until now.

21 (Laughter.)

22 Q How long ago was that?

23 A That probably was 20 years ago.

24 Q And it will probably be 20 years before
25 you --

GRIFFIN - DIRECT

1 A Well --

2 (Laughter.)

3 Q Did you ever work though, besides
4 testifying, did you ever work on litigation involving
5 MMR vaccine?

6 A As I say, I have studiously avoided any
7 request to get involved in any kind of legal issue
8 ever since my first experience, really until this came
9 along, and I just thought it was such an important
10 issue to make sure that we get it right, that I
11 agreed. So this is one of three things I've been
12 involved with with respect to MMR.

13 Q The other two, one of them was in the United
14 Kingdom?

15 A Right. So I was involved in the U.K.
16 litigation or failure of litigation. Putting together
17 the information at least for the judge in that case.

18 Q The information on measles virus --

19 A On measles vaccine, right.

20 Q The other piece of litigation that --

21 A The other, and that is still pending.
22 There's at least one case pending against Merck that
23 I've consulted with them on and written an expert
24 testimony on that's here in the U.S.. I think
25 independent of this. I don't know exactly how they

GRIFFIN - DIRECT

1 fit together. But that hasn't gone to trial yet. I
2 don't know what the status is.

3 Q I'd like to talk now a bit about measles
4 virus, and right now, until I change we're going to be
5 talking about wild measles virus.

6 Can you tell me how wild measles virus is
7 spread? And we're going to put up a slide here, I
8 think.

9 A The spread in a population is a respiratory
10 spread. So basically people shed the virus in their
11 respiratory tracts and that's how people, it's a very
12 infectious virus. It's one of the most infectious
13 agents that we have, the wild-type virus.

14 Q This slide we put up is Slide 1. So far Dr.
15 Griffin has not talked about that yet.

16 A No.

17 Q Feel free, I just was giving you the opening
18 to talk a little bit about wild measles virus. It
19 spreads by --

20 A It spreads through the respiratory tract, so
21 basically by respiratory droplets and being exposed to
22 someone. So it's similar to the way influenza would
23 spread or actually chicken pox spreads the same way.

24 So you breathe in the virus and, as I say,
25 the wild-type virus is very infectious which is

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1 interesting. It's very difficult to grow it in tissue
2 culture, but it knows how to infect people. We don't
3 completely understand how it's so efficient at getting
4 from one person to another, but it definitely is.

5 Q After it enters a human, what happens next?
6 And if you'd like to refer to the slide at this point,
7 feel free, if it helps.

8 A This is actually from my chapter in "Fields
9 Virology" on measles to try to give the idea of the
10 pathogenesis.

11 Basically it affects the respiratory
12 epithelium, so it's the initial cells that it comes in
13 contact with in the respiratory tract. Then from
14 there it goes to, it's carried to the local lymph
15 nodes. So the lymphatic tissue that drains the lungs.
16 A lot of this we know from studying children, but we
17 also know this from studying monkeys. This is a virus
18 that's very restricted to humans, but it does also
19 affect non-human primates and causes measles. All
20 other animal models actually are not, I don't think
21 they're useful for studying measles. Monkeys are and
22 people are obviously.

23 From the local lymph nodes, and this is a
24 very lymphotropic kind of virus, it then spreads from
25 the blood. So cells that get infected in the lymph

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1 nodes and can leave the lymph node, that's what we
2 call a cell associated viremia in the blood. So it's
3 in lymphocytes and monocytes are the main cells that
4 are infected that are circulating in the blood, and
5 undoubtedly the main cells that are infected in the
6 lymph node as well and other lymphoid tissue.

7 Once it gets into the blood it spreads
8 everywhere. We know it spreads to the skin because
9 you get a rash. But there are often liver
10 abnormalities, there can be cardiac abnormalities. It
11 can certainly spread to the gut. As I say, you find
12 it in lymphoid tissues everywhere, but also it affects
13 endothelial cells and epithelial cells in addition to
14 the lymphoid types of cells. So because it does that,
15 you can find it in many organs.

16 Q Now, Doctor, on the bottom of Slide 1, you
17 have a series of numbers. What do those numbers
18 represent?

19 A Those are days after infection. As you'll
20 see from a couple of subsequent slides, the line is
21 sort of the amount of virus. It's a crude estimate of
22 the amount of virus. So as it's spreading, you're
23 increasing the amount of virus that's present in the
24 body in general. Then you can see the line then goes
25 down. That's around, the peak of the viremia and the

GRIFFIN - DIRECT

1 spread is around somewhere between 9 and 14 or 15 days
2 typically.

3 Q Again, this is with the wild virus.

4 A This is with the wild virus. This is
5 everything with the wild virus. Right.

6 Then it starts to get cleared. Then that's
7 a manifestation of the immune response once it starts
8 getting cleared.

9 Q You mentioned that it's specific to humans
10 and some non-human primates. Then you said you didn't
11 think other models of other viruses were that helpful
12 or useful.

13 A That may be my bias.

14 (Laughter.)

15 Q What do you mean by that?

16 A What I mean by that is that there are,
17 monkeys get a disease that is in every way similar.
18 They get a rash, in every way it's similar, spread by
19 the respiratory tract, et cetera, as humans get. But
20 it's hard to study monkeys and it's also hard to study
21 people. So most people if they want to study this
22 interesting virus would like to study something
23 smaller. A mouse would be nice. Unfortunately the
24 receptors that measles virus uses are, and we'll talk
25 about this later, user probably two or three different

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1 receptors, aren't present in mice. Therefore the mice
2 don't really get infected. You can sometimes put it
3 in through the brains and get, which is not exactly a
4 natural route of transmission for the virus.

5 People have made what they call transgenic
6 mice which is to put the human receptor into the mouse
7 to see if now they could get a measles-like disease,
8 but still the replication is very restricted and
9 again, doesn't mimic, you can't use a respiratory
10 tract route, et cetera. It just doesn't mimic the
11 disease.

12 Q Do you think that using, I may get the names
13 screwed up here, but do you think that morbilliviruses
14 compare to measles virus readily in terms of how
15 similar they are, what results can be expected?

16 A Measles is within a subgroup of the paramyxovirus
17 variety, which includes a number of interesting human
18 pathogens like mumps, for instance, like respiratory
19 syncytial virus. But within the morbilliviruses,
20 measles is the human version, the morbillivirus is.
21 As I mentioned, they're very species specific, all of
22 the morbilliviruses.

23 There are morbilliviruses that infect dogs,
24 canine distemper; seals. The one that's most closely
25 related to measles actually is rinderpest virus which

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1 causes a disease in cows. So it's thought that the
2 origin of measles was moving, was a transfer from cows
3 in early herding societies into human. Whether that's
4 the case or not, I don't know.

5 Those are interesting viruses. We certainly
6 learn from studying them and they cause interesting
7 diseases in their own particular hosts, just like
8 measles does in the human host.

9 Q But measles are specific to humans?

10 A It is. And monkeys. Because monkeys can
11 get it naturally from humans.

12 Q You mentioned that it hits the lymphatic
13 tissue. Would that mean that it's lymphotropic?

14 A Well, yes, that certainly is a primary site
15 of replication is in lymphoid tissue, but it's
16 certainly not the only site. As I say, it also
17 replicates in epithelial cells and in endothelial
18 cells. We think we know the receptor for the
19 lymphoid, a lot of the lymphoid replication, which is
20 a receptor known as SLAM for this wild-type virus, but
21 we don't really know how it gets in and what the
22 receptor is in epithelial cells of endothelial cells,
23 but those are clear targets for the virus.

24 Q Does it preferentially select tissue in the
25 gut?

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1 A No, as I say lymphoid tissue anywhere and it
2 will infect epithelial cells any place, both of which
3 are represented in the gut.

4 Q So it just spreads throughout the body.

5 A Yes. In fact I don't even think gut made my
6 slide here, but it could be included as could the
7 heart which also isn't on there.

8 This is a systemic virus infection.

9 Q What about the brain then?

10 A The brain is interesting. We've done a
11 number, again, in connection with studies that we did
12 in Peru, we did autopsy studies of children who were
13 dying with measles acutely specifically to look to see
14 where the virus is. We found it in all these places,
15 the usual suspects. But when we looked in the brain,
16 we could find it only in endothelial cells. So we
17 could find brain vessels. The lining of the vessels
18 infected in a few people that we looked at. We didn't
19 find it initially, they use a pretty sensitive
20 technique, to be able to find that. But we never
21 found it in actually the brain tissue itself. It was
22 just in the vessels.

23 Q But it was found throughout the --

24 A Well, no, no. It was one here -- You could
25 find A positive vessels, put it that way.

GRIFFIN - DIRECT

1 Q In these patients where you found it -- let
2 me step back. You found it in the blood vessels in
3 their brain?

4 A Right.

5 Q You didn't find it elsewhere in their brain?

6 A No place else in the brain. And that was
7 also true of the patients, as I mentioned that we were
8 studying that had this post-infectious
9 encephalomyelitis. Actually we couldn't find it any
10 place in those individuals, but presumably they did
11 have this vascular or endothelial lining infection
12 earlier and it was just gone.

13 Q But could you find it in the same patients
14 in other tissue in their body?

15 A Oh, sure. Yes, it was much easier to find
16 elsewhere. We had a harder time finding it in the
17 brain.

18 Q Was it widespread?

19 A Oh, yes. The spleen, the lungs, the skin.
20 Most places, the gut. Most places we looked you could
21 find it, particularly if you looked in lymphoid tissue
22 that was associated with that particular organ. But
23 we found it in the liver. It was very widespread.

24 Q When you looked in the brain did you see it
25 in the neurons?

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1 A No. As I say, it was only in these vascular
2 endothelial cells. It looked like it was unable to
3 spread out of that spot.

4 Q And I take it then not the astrocytes or the
5 microglial --

6 A Not in, we're talking about acute wild-type
7 measles. We have a different story with SSPE and
8 other neurologic complications, but for acute measles
9 you don't find it.

10 Q I want to turn now to the clinical symptoms
11 of wild measles virus infection. If you could talk
12 about those please, and what's going up now in front
13 of the Court is Slide 2, and feel free to refer to
14 that at any point during your discussion of the
15 clinical symptoms of elucidates the discussion.

16 A We'll put all this together at the end, but
17 the clinical symptoms, the way that measles is
18 recognized is usually with a rash. And so clinical
19 measles gets diagnosed. An astute physician in an
20 outbreak situation may be able to see Koplik's spots
21 which are little spots on the inside of your mouth in
22 children who come in with a fever.

23 As you can see, the black line is the fever.
24 As I mentioned earlier, the peak of the viremia is
25 occurring around between days 10 and 15. During that

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1 period of time is also when you start to see the
2 earliest symptoms.

3 So one point is the first ten days of
4 infection are relatively asymptomatic. There's a lot
5 of virus replication going on of symptoms until
6 usually the prodromal period which is maybe for two or
7 three days before the onset of the rash when there is
8 fever, there can be conjunctivitis, cough, some, we
9 call them prodromal symptoms before the rash appears.
10 Then the rash appears and it's three or five days of
11 rash is typical.

12 Q If I take it from this slide, when the rash
13 is appearing is that really towards the end part as
14 the infection has started to clear?

15 A Yes. In fact it correlates with -- The
16 onset of the rash correlates with the initiation of
17 appearance of the adaptive immune response and the
18 initiation of virus clearance is occurring during the
19 rash phase.

20 By the time the rash is over, the fever is
21 over, usually the child feels, assuming no other
22 complications, feels perfectly fine. Home.

23 Q And the line on the bottom, the numbers on
24 the bottom again are --

25 A Days after infection

GRIFFIN - DIRECT

1 Q Do you see diarrhea as one of the clinical
2 symptoms of measles infection?

3 A Diarrhea is not uncommon, and it really
4 depends a lot on what population you're studying. As
5 I say, the populations that we've studied in most
6 depth are in developing countries, either in Peru or
7 in Africa. But we certainly have done some studies
8 within the U.S.. But in Peru where we did the most
9 in-depth studies, diarrhea was very common but it was
10 almost always due to another infectious agent. It
11 might be salmonella, it might be shigella, it might be
12 entamoeba histolytica. There were lots of things that
13 caused diarrhea in those --

14 Q That last one's going to give the court
15 reporter a fit. We'll spell it afterwards.

16 A But all I'm saying is that in those
17 populations diarrhea is a common -- there are a lot of
18 things that cause diarrhea in that population.
19 Basically what the children with measles got that got
20 diarrhea, they generally reflected what was going on
21 in the general population. So if there was a
22 salmonella outbreak, then they were more likely to
23 have that, et cetera.

24 But usually the diarrhea could almost always
25 be ascribed to another diarrhea-causing agent that was

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1 there at the same time.

2 Q If I take that right, then the diarrhea
3 wasn't necessarily caused by the measles, but rather -
4 -

5 A No. Diarrhea isn't a very common symptom of
6 measles per se. And certainly if you look at
7 populations in more developed countries that have less
8 problem with diarrhea causing agents, then, I won't
9 say diarrhea is never seen, but it's not considered a
10 common aspect of measles.

11 Q I want to turn to the immune system because
12 we touched on it a little bit already. It's important
13 obviously to this case.

14 If you could take us through sort of the
15 timeline of what's happened with the immune system
16 after the introduction or after the virus infection
17 with wild measles virus. And sort of explain, we've
18 gone to Slide 3 here, and it's the same format as the
19 other two. If you could just take us through and tell
20 us about the different parts of the immune system that
21 are coming into play here.

22 A Right. The initiation of the immune
23 response, what's here is pretty much what you can
24 measure in the blood of an individual with measles.
25 But the initiation of the immune response is really

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1 starting at the time of the initial infection of the
2 lymph nodes after the respiratory infection. So it's
3 happening back at day one on this graph, although
4 there is nothing in here that shows that.

5 There are cells that are resident in lots of
6 places, but certainly in mucosal tissue like the
7 respirator tract, dendritic cells that pick up
8 pathogens. I mean their job is to take up pathogens
9 that have been introduced wherever. It could be the
10 gut, it could be the skin, it could be the respiratory
11 tract. And carry those to the lymph node where
12 actually you initiate the immune response. So these
13 are what we call antigen presenting cells. These are
14 cells that know how to process and present antigen and
15 start stimulating T cell responses within the lymphoid
16 teacher.

17 So probably what's going on in the lymph
18 nodes during those first few days is quite complicated
19 because we know the virus is replicating, but we also
20 know that the immune response that's being initiated,
21 cells the virus are replicating in are going out into
22 the blood. But eventually you build up enough of an
23 immune response. So you're stimulating, on this
24 diagram we're talking most about T cells, CD4 and CD8
25 T cells which are getting stimulated by the measles

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1 antigen. So within the whole immune repertoire we
2 have a small number of cells that will actually know
3 how to recognize measles virus. So what you want to
4 do in an immune response is to greatly expand those
5 few cells that may be present and are measles virus
6 specific as part of the normal repertoire.

7 So what's happening in those first seven or
8 eight days is this really amplification of those cells
9 that are specific. It's happening both for CD4 T
10 cells, it's happening for CD8 T cells, and it's also
11 happening for B lymphocytes that would be specific for
12 the measles virus antigen. All of this is gearing up
13 to have an adaptive immune response that is going to
14 allow clearance of the virus.

15 Q Just for the record, Respondent's Exhibit D,
16 I believe is Dr. Griffin's report.

17 Just to make sure I have a good
18 understanding of what's happening with the T cells, in
19 your report you were talking about naive cells and
20 differentiation. Is that what you're talking about
21 here?

22 A Exactly. They start out, the cells start
23 out naive in that they have never seen measles before.
24 And so now what you want to do is select those cells
25 that know how to respond to measles and that's done

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1 through this antigen presenting cell process which is
2 very complicated in stimulating the cells to
3 proliferate, producing cytokines that allow them to
4 proliferate. There's a lot of things going on to
5 allow that expansion to occur, and for that expansion
6 to be of the cells that are specific for measles
7 virus. The ones that are going to be relevant to
8 actually recovering from this infection.

9 Q So essentially the body starts saying we
10 need to gear up this particular kind of cells to go
11 after --

12 A Absolutely. Measles is a major challenge,
13 the wild type measles is a major challenge to the
14 immune system. In fact it was Burnett I think that
15 says it was nature's way of figuring out who was
16 immune deficient.

17 Consequently, it invokes a substantial
18 immune response to the virus as part of that process.

19 Q What's the IgM and the IgG specify? What
20 does that signify with the immune response?

21 A In addition to the T cell response which was
22 crudely diagramed here as CD4s and CD8s, you also get
23 an antibody response. And as I mentioned, T cells are
24 amongst the cells that are being stimulated in the
25 lymph node by the measles virus antigen resisting

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1 cells. then the first kind of, and they also go
2 through phases of development. The first phase is
3 that they can make IgM. That's the first kind of
4 antibody they can make, and they have to go through a
5 differentiation process in order to make IgG which is
6 what's going to be the long term response to measles,
7 is measles IgG. That process of switching from IgM to
8 IgG, particularly the very mature IgG response is a T
9 cell dependent process. So these two things are
10 intertwined. To get long-lived memory IgG you need T
11 cells. In addition, T cells are doing their own thing
12 with respect to virus clearance as well.

13 Q That's a concept I don't think we've heard
14 before. In what way are the T cells helping the body
15 switch over to IgG if you can explain in a form that's
16 easy for us to understand.

17 A There's two processes of differentiation for
18 B cells to be able to go from IgM secreting cells to
19 what I would call mature plasma cells that are making
20 antibody. For protection from reinfection, which
21 measles is fantastic at. I mean you have lifelong
22 immunity to measles once you've recovered from this
23 infection.

24 Q Because of the IgG?

25 A Mainly because of the IgG. So to get that

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1 long term secretion of IgG in the most mature form,
2 two things have to happen to B cells. They're called
3 class switch recombination and affinity maturation.
4 Class switch recombination is moving from IgM to IgG
5 and there are several types of IgG and you can also
6 make IgA, but that actually involves a deletion. But
7 that's a T cell dependent process to reorganize
8 basically the DNA of those B cells so they now make
9 IgG instead of IgM.

10 So the naive ones have IgM on their surface
11 and they are of all different varieties. Now what you
12 do is select the ones that are reacting with measles.
13 They then get transferred to another place actually in
14 the lymph node, the germinal center, where these
15 maturation processes go on.

16 Affinity maturation takes a longer period of
17 time and isn't totally independent but sort of
18 independent of class switch recombination in that you
19 select, progressively select the cells that make the
20 best antibody. The ones that have the highest
21 affinity for the antigen. That process actually
22 occurs over months if you follow affinity maturation
23 after this stage. That's also a T cell dependent
24 process. That's what's necessary for the long term
25 secretion of IgG after infection.

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1 Q So basically you've got T cells working
2 here, they're working in combination with your
3 antibody response. Your IgM is kind of a first
4 antibody response, but then after that it starts
5 switching over to IgG. Is that pretty much what's
6 going on?

7 A Right. And the IgM can be neutralizing.
8 It's probably very important to help restrict virus
9 spread in the body after you initiate the
10 immunoresponse. So that's an important component.
11 But it won't be long term. It might help you with the
12 acute phase but it's not going to protect you from
13 reinfection because it won't be around a long time.

14 Q You have a line here at the bottom that says
15 immune suppression. What's that representing as far
16 as the immune responses?

17 A That's one of the reasons we're sort of
18 fascinated with measles. It's a very paradoxical kind
19 of concept. At the same time all this is going on
20 with measles, so you've got all these CD4 cells and
21 CD8 T cells and antibody secreting cells, et cetera,
22 being produced against measles. At the same time that
23 the immune system is not responding normally to other
24 challenges.

25 So most of the deaths due to measles are due

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1 to other infectious diseases. Diarrhea was one
2 example. For the most part that's not a fatal,
3 diarrhea isn't a fatal complication, but pneumonia can
4 be. All autopsy studies that look at what causes the
5 death of children with measles show that what causes
6 the death of children with measles are other
7 infections, usually pneumonia. It's often bacterial
8 pneumonia, it could be other viruses, but usually it's
9 bacterial pneumonia.

10 So there is a period of time which is
11 initiated during this acute phase that children are
12 more susceptible to other infectious diseases. So
13 this is a very clinically important complication or
14 outcome or by product of measles and all of the data
15 suggests that it's directly related, as I say
16 paradoxically, to the fact that the immune system is
17 so activated and so engaged in making an immune
18 response to measles that it is not appropriately
19 positioned to respond to some new challenge that comes
20 along at this same time.

21 Q So in fact the immune system is working
22 really well in this against measles, but it's --

23 A Right. As I say, that's one of the puzzles
24 of this, why it's intriguing to us from a biological
25 perspective to try to understand exactly what's going

GRIFFIN - DIRECT

1 on. It's complicated and we don't have all the
2 answers, but those are the facts.

3 Q One of the concomitances that it leaves the
4 body more susceptible to other --

5 A Other infectious diseases. But at the same
6 time you're getting this -- I mean the immune response
7 to measles is one of the best, as I say it gives you
8 lifelong immunity. There have been studies that show
9 on island populations that 60 years later if you
10 recovered from measles, you're still immune to
11 measles. So it's terrific.

12 Q We've been talking about each of these three
13 different things, the replication and what's happening
14 in the body, what's happening outside the body in
15 terms of clinical responses, and what's happening with
16 the immune system separately.

17 I know we've put these all together to sort
18 of show one right on top of another so we can see
19 what's happening overall. This is Slide 4.

20 A The main point of this in addition, just so
21 you know what's going on with the virus replication,
22 you know what's going on with clinical symptoms, and
23 you know what's going on with the immune response is
24 the fact that the rash is dependent on the immune
25 response. It comes at the same time as the immune

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1 response. Children who are immunosuppressed for
2 whatever reason, HIV infection or whatever, can get
3 measles without getting a rash. If they don't make a
4 good immune response to measles, they won't get a
5 rash, so it makes it hard to diagnose because that's
6 usually the way we diagnose measles is with a rash.
7 At the same time as the appearance of the rash which
8 is coincident with the appearance of the immune
9 response, you're getting clearance of the virus. So
10 that period of time is the real manifestation of the
11 measles specific immune response and virus clearance
12 that are occurring during that period.

13 Q Is fever in any way related to the immune
14 response?

15 A Oh, yes. That's when you see fever. You
16 see fever during this rash period or just before, so
17 that's my little line there that goes up just before
18 the rash. Often there's fever for a day or two prior
19 to the onset of the rash, but that is a manifestation
20 of the immune response also. In fact, again, children
21 who are immunosuppressed and so are not mounting this
22 kind of an immune response to measles often do not get
23 a rash, but they're often thought to have had very, if
24 they're even recognized to have measles, it's said to
25 have been very mild, that they weren't really very

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1 sick. In contrast, I don't know how many people in
2 this room have had measles, but most people who had
3 natural measles remember it. It's one of those
4 diseases that you remember because it's a very, you're
5 really sick. You're in bed for a few days. It's just
6 an unusual observation that if you don't get a very
7 good immune response because of whatever congenital
8 thing, you won't get as much fever, you may not even
9 get a rash at all, so measles will appear to have been
10 very mild.

11 Q With respect to, switch back to the immune
12 system. You in your report had explained different
13 phases to the immune response.

14 We've gone to Slide 5 now. This may help
15 take us through the different phases.

16 A This isn't my diagram, this is a rather
17 classic diagram of what happens during a viral immune
18 response, but I think it's very relevant to discussing
19 the immunologic aspects of this particular case
20 because the immune system is not static. The immune
21 system is changing all the time, and that's perfectly
22 appropriate. This diagrams the kinds of things that
23 are going on during a virus infection. This is just
24 sort of a generic virus infection. So we talked a
25 little bit about this in the measles context, but the

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1 beginning is the entry of the virus, as you can see on
2 the far left, and then these innate defenses. And
3 there are a number of innate defenses that can come
4 into play for virus infections. One of them, there
5 can be production of cytokines. The most important
6 cytokine for most viral infections that help to sort
7 of restrict virus replication is a production of
8 interferon. Interferon is very commonly produced
9 during some of these early phases.

10 It may not be produced, we can't find it in
11 measles. So a number of viruses that are particularly
12 pathogenic, actually, have figured out how to block
13 the interferon response in order to have a better
14 chance of really causing a more severe disease. And
15 wild-type measles appears to be amongst those viruses
16 that can do that.

17 But you're marshaling macrophages. There
18 are cytokines being produced that are important for
19 the development of the T cells, et cetera, so the
20 early phase of innate defenses and induction of the
21 adaptive response are all sort of blended together.

22 Q Is this what you'd describe as the initial
23 phase or the first phase?

24 A Right. This is the initial phase.

25 One of the important things during that

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1 induction of the adaptive response and during the
2 adaptive response is that you produce very large
3 numbers of virus-specific lymphocytes, both CD4 and
4 CD8 cells, undoubtedly in the lymphoid tissue we can
5 measure it most easily in the blood, so a very large
6 proportion of the T cells that are circulating may be
7 directed against measles. We're all challenged with
8 all sorts of different -- We need cells that do other
9 things, not just measles.

10 So one of the things that happens during
11 this late phase is, the memory phase, is that you have
12 to shut off that immune response. Once the immune
13 response has sort of done its job and cleared the
14 virus, then you need to decrease the number of cells
15 that are actually specific for that particular virus.

16 That dramatically decreases ten-fold at
17 least. Then you're left with, this is the last phase,
18 which is called the memory phase. There will be a
19 much smaller population of cells than there was at the
20 peak that are those memory cells that stay there, they
21 continue to circulate. They're the antibody secreting
22 cells that we talked about. That's one group. They go
23 mostly to the bone marrow, but there are also T cells
24 that are memory cells. If that individual meets the
25 measles virus again, then those cells go back into

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1 action basically

2 Q So far we've just been talking about the
3 wild virus. I want to turn now to the vaccine virus,
4 the attenuated virus. Basically we're going to talk
5 about how it may be different from the wild measles
6 virus. What does it mean when one says attenuated
7 virus? What does that mean

8 A That means a virus that's lost its
9 virulence. Usually it's been specifically attenuated,
10 so virulent virus by definition here is a virus that
11 can cause the disease measles. The attenuation
12 process that was used in measles, it's probably
13 similar. It was a very classic --

14 Q This is how they made --

15 A This is how they made the vaccine, to make
16 the vaccine virus. As I mentioned, the virus is
17 specific for, it's a very human primate tropic virus
18 basically. The process of adaptation for this virus
19 was to adapt it to grow in the non-human cell.

20 The idea was if it now learned how to grow
21 in something else, in the measles case it's chicken
22 cells, so they adapted it to grow in chicken embryo
23 fibroblast. Once it now grew very well in chicken
24 embryo fibroblast, it no longer grew so well in human
25 cells.

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1 So one of the things that it's done is
2 actually changed the kinds of receptors that it can
3 use and as I say, I don't think we still know what the
4 receptor is on chicken cells, but there's a CD46 which
5 was the first receptor that was recognized for
6 measles, is actually recognized mainly by the vaccine
7 virus and really not by the wild-type virus.

8 Q What was the wild-type virus receptor?

9 A SLAM. CD150 if you want a CD number.

10 Q And the vaccine is 46?

11 A CD46. That was the first receptor that was
12 recognized, and that's not surprising because as I
13 mentioned at the beginning the wild-type virus doesn't
14 grow very well in the kinds of cells that we use in
15 tissue culture. It's a pain to get enough of it.

16 So the viruses that grow very well and that
17 everybody studies because they're easier, are these
18 tissue culture adaptive strains or vaccine strains for
19 the most part. So a lot of the literature on the in
20 vitro studies of measles are really the vaccine strain
21 of measles because you can work with it much more
22 easily than you can with the wild-type virus.

23 Q You were mentioning that it's changed its
24 properties now and I think you were saying it doesn't
25 replicate as well?

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1 A It doesn't replicate nearly as well when you
2 inoculate it into a person or a monkey. So it
3 replicates to a much lower degree. As I say,
4 paradoxically, if you look at it in tissue culture it
5 replicates better than the wild-type virus so there's
6 clearly something we don't understand here. But if
7 you look at it in a person or a monkey, the replication
8 is almost, the viremia is almost undetectable for a
9 vaccine strain of virus compared to the wild-type
10 strain which causes this huge viremia.

11 Q I think you had a representation of that.

12 A I do.

13 Q This would be Slide 6.

14 A This was an experimental study that we did
15 which was comparing lots of strains of measles virus.
16 It was during a time that we were trying to identify a
17 strain that we could use to infect monkeys that would
18 give us disease, that would give us a rash and a
19 viremia. So this is just the number of infected
20 cells, basically, in the blood. The big peak, which
21 is labeled wild-type is the kind of viremia you get
22 when you inoculate the wild-type virus into a monkey.

23 There's another tissue culture adapted wild-
24 type strain which is not completely attenuated, gives
25 us the middle thing. Then there's a whole bunch of

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1 vaccine and vaccine-derived strains which are all at
2 the bottom. It was only every once in a while in one
3 or two monkeys on one day or another that one might be
4 able to detect measles virus. So the amount of
5 replication of the virus is very much decreased
6 compared to what happens with the wild-type virus.
7 That was one of the things, many things were probably
8 accomplished with attenuation, but this is probably
9 the most critical in that it no longer really caused
10 measles, but it replicated enough that it induced an
11 immune response to measles.

12 Q And Bilt stands for?

13 A Bilthoven is a town in Holland where the
14 virus came from. In Chicago 1, it was during the
15 outbreaks in the United States in '89 to '91. That
16 was a wild-type virus that was isolated then, but
17 subsequently has been adapted to grow in tissue
18 culture. Bilthoven we can only grow in cord blood,
19 mononuclear cells. If we grow it in anything else it
20 becomes attenuated. It loses its ability to cause
21 disease.

22 Q You talked about the receptors. Can you
23 predict based on what you know about the differences
24 that you talked about between the wild-type and the
25 vaccine type, can you predict sort of differences in

2778A

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1 clinical presentation or immune response?

2 A Well --

3 Q Between the two.

4 A The vaccine strain generally doesn't cause
5 disease. And we're also inoculating it subcutaneously
6 and the natural infection is obviously coming in by
7 the respiratory route. There's no evidence of
8 transmission of the vaccine virus from one person to
9 another, in contrast to the polio virus vaccine or
10 something, other live virus vaccines sometimes are
11 transmissible from one individual to another. But
12 that's never been demonstrated for measles, and it's
13 probably just because it doesn't replicate in the
14 respiratory tract very well.

15 Even for wild-type measles, all the major
16 respiratory infection is occurring during that period
17 of disease rash, even though it comes in through the
18 respiratory tract it has to actually circulate back to
19 really get a lot of virus production in the
20 respiratory tract itself. For that person, the person
21 doesn't become infectious for another individual until
22 that, just a few days before the rash onset.

23 Q Would you expect the complications of wild
24 virus to be the same as those you'd seen in vaccine
25 virus based on the differences you've observed?

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1 A I certainly wouldn't think that you'd see
2 anything with the vaccine virus that you hadn't seen
3 with the wild-type virus. As a recognized
4 complication of wild-type measles.

5 But I think you would expect that the
6 complications would be dramatically diminished, and we
7 know that, for the vaccine virus. There is no
8 clinically important immunosuppression that occurs, no
9 increased susceptibility to other infections, so the
10 manifestations, a small percentage of children, and
11 this child was one of them got a rash after measles
12 vaccine, so that's maybe ten percent of people will
13 get a rash. Most children get some fever actually,
14 and it's again, five to fifteen percent that get a
15 fever of 103 or more. So to get a fever that would be
16 considered significant. But still that's a small
17 proportion, but it's also a large proportion of people
18 who, of children who get a rash and fever, this
19 particular, with the current vaccine. But as I say,
20 the important components of measles and the
21 complications of measles don't occur with the vaccine.

22 Q One of the components that's had a lot of
23 focus here of at least the wild viruses,
24 immunosuppression, we talked about that. Do you see
25 that immunosuppression with the vaccine virus?

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1 A As I mentioned, you don't see clinically
2 relevant immunosuppression. Immunosuppression in
3 wild-type measles, the reason that we focus on it is
4 because of this increased susceptibility to other
5 infections. That's why it's important. It's not
6 important because you lose skin test responses or
7 because your lymphocytes don't proliferate very well
8 in vitro, and there's lots of laboratory
9 manifestations of the immunosuppressant during wild-
10 type measles.

11 If you take the lymphocytes of somebody who
12 has been vaccinated with the measles vaccine and then
13 look for any laboratory evidence of changes in the
14 lymphocytes that are circulating, you could find
15 those. They're not nearly so profound or as easily
16 found or as reproducible as they are in the wild-type
17 disease. But you're inducing an immune response.
18 That's the reason to give a vaccine, is to induce an
19 immune response to measles. So that's happening and
20 you can document that by looking at the changes in
21 the cells that are occurring or present in the blood.

22 Q Do you see an increased susceptibility to
23 infection after vaccine?

24 A No, there's no evidence of that and that's
25 been looked for quite carefully in quite a few studies

2781A

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1 to try to look and see if there is any increased
2 susceptibility to other infections. No study has
3 found that. There's just no clinically important,
4 there's not really immunosuppression in a meaningful
5 way that occurs with the vaccine, put it that way.

6 Q Does the vaccine virus, the
7 immunosuppression that goes along with it, seem to
8 impede the body from clearing the vaccine virus?

9 A No. As I say, I wouldn't call what the
10 vaccine does immunosuppression. Again, it depends on
11 how you're going to define the term, but there are
12 some immunologic changes that occur coincident with
13 the vaccinations, which are also coincident with
14 inducing the immune response to measles.

15 Q Turning to the specific facts of this case,
16 on December 20, 1995 Michelle Cedillo received an MMR
17 vaccine. From what you've seen, is there any evidence
18 that she mounted a normal immune response to that
19 vaccine?

20 A There are a couple of pieces of evidence.
21 First of all, she got a fever and a rash which is a
22 manifestation of the immune response. But more
23 importantly, she got an IgG response which was still
24 present at least two years later which is when it was
25 looked for, which means she established this memory

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1 immune response which requires both CD4 cells and
2 antibody as a part of that memory response, and if you
3 don't get a good immune response to the measles
4 vaccine the usual evidence for that is lack of
5 antibody response or lack of an IgG response to the
6 vaccine.

7 Q I take it from what you just said that the
8 fever and the rash that Michelle had about seven days
9 afterwards, you're attributing to the vaccine?

10 A I think that makes a lot of sense. There's
11 no way to be sure.

12 Q There's been an assertion that measles virus
13 in the gut could attach to monocytes or macrophages in
14 the blood and enter the brain?

15 A I don't understand how that is going to
16 happen. There's basically, there's antibodies present
17 which is going to prevent the virus moving from one
18 cell to another. That's an antibody's job is to
19 neutralize that virus from infection. The thought
20 that it would attach to the outside of a cell and then
21 move into the brain, I guess I just don't see why that
22 would be happening.

23 Q There's a claim in this case that the
24 vaccine strain, measles virus, was able to persist.
25 One piece of evidence that's being looked at is what

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1 is purported to be the recovery of measles virus RNA
2 by way of PCR testing, from a gut biopsy sample.

3 I know you've discussed PCR, your own
4 concerns about the PCR testing in your report on page
5 seven, and I don't want to go back through that
6 because the Court has already heard a lot of testimony
7 on PCR.

8 What I'd like you to focus on is one aspect
9 of the PCR test result in this particular case that I
10 think you had some concerns about, and that is the
11 copy numbers. What is the significance of copy
12 numbers in the Unigenetics test results to you?

13 A The only shred of evidence as far as I can
14 tell that measles would have anything to do with this
15 child's disease is that one piece of PCR data. That
16 has to be looked at carefully. As you already said,
17 there's already been plenty of testimony, which I
18 wasn't here for, but I've heard about, that would call
19 into question the laboratory and the data, et cetera.

20 In addition what leaps out at me is that
21 it's not a biologically plausible number. That many
22 copy numbers of a virus in the amount in the tissue
23 that they looked at would mean that it would have to
24 be an overwhelming infection. It would have to be
25 more virus replicating in that piece of

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1 gastrointestinal tissue that was biopsied than is
2 present at the peak of wild-type measles virus
3 infection.

4 The fact that there's no pathology that's
5 similar to measles. I mean measles pathology is very
6 characteristic. It causes syncytia, it causes
7 inclusion body formation, it would cause inflammation.
8 There are a lot of things you would expect to see if
9 you have that much measles virus infection in a piece
10 of tissue.

11 To me, that just wasn't a biologically
12 plausible number and would be one that would be called
13 into question. I'd like to see a repeat, or to know
14 that they were able to amplify it. If they had that
15 much virus they ought to be able to easily amplify it
16 from other portions of the genome, not just that one
17 primer set that worked. If you have a lot then
18 there's no problem with being able to, frankly you
19 probably ought to be able to isolate it and grow it.
20 But most people don't try to do that. But you ought
21 to be able to stain for it, you ought to be able to
22 see it making protein if there's all that much virus.
23 You ought to be able to see it by lots of different
24 ways than just a PCR number.

25 Q Would you expect to see it in other places?

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1 A I can't imagine why in the world it would
2 only be in the gut, but yes. If you have that much
3 virus in one place it's hard to imagine why it would
4 be only in that one little spot.

5 Q I know measles, we've already heard
6 testimony, measles virus is known to persist on
7 occasion in humans. Can you describe what happens
8 when measles virus persists in a human?

9 A Yes. There are well characterized diseases
10 that are associated with measles virus persistence, so
11 there's no doubt that that can happen. The most
12 classic example is subacute sclerosing
13 panencephalitis, SSPE, but there's also -- well, we'll
14 discuss SSPE first. That's wild-type measles that
15 does that.

16 Q It's not known to occur with vaccine virus?

17 A No, in fact all cases of SSPE for which
18 there has been suspicion that it has been caused by
19 the vaccine virus have all been proved to have been
20 caused by the wild-type virus.

21 In that case what I think happens, we don't
22 really know because SSPE occurs 7 to 10, the clinical
23 symptoms of SSPE occur 7 to 10 years after the measles
24 virus infection, and it's a relatively uncommon
25 complication, maybe 1 in 10,000 children. And it's

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1 mainly children that got there wild-type measles
2 infection at a very young age. So most of the cases
3 are children, when people can document when they got
4 their measles, they were less than two at the time
5 they got the wild-type infection.

6 Then they're normal, or apparently normal,
7 for year until there start to be some usually
8 deterioration in school performance and that sort of
9 thing or some other first signs or symptoms of the
10 disease. And at that time when the persistent
11 infection which is in the nervous system is diagnosed,
12 it's very widespread.

13 So my assumption of the pathogenesis, and as
14 I say, we never are able to look, we don't have any
15 animal models for this and we can't identify these
16 kids at the time they get their infection and then
17 find out what's happening, is that the virus probably
18 enters the brain in those children at the time of the
19 original infection. Again, often these children are
20 said to have had mild measles, so you wonder whether
21 they mounted a really appropriate immune response at
22 that time. Then the virus, it must just replicate
23 very slowly and spread very slowly through the nervous
24 system through all those years and eventually the
25 thought is it builds up to a threshold that is enough

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1 damage and enough virus replication that there are
2 some symptoms.

3 Once that occurs, as I say, the virus is
4 very widespread and essentially all of those children
5 die, usually within a year or two of the onset of the
6 neurologic symptoms.

7 Q What are, you mentioned some intellectual
8 deterioration. What are the other --

9 A Intellectual deterioration. There are
10 movement disorders. One thing that's known as
11 myoclonus is a common one. They eventually become
12 mute and bedridden. Really pretty profound and
13 progressive change over that period of time. There's
14 characteristic EEG abnormalities, what they call birth
15 suppression pattern. So one of the ways of trying to
16 diagnose it is that way. Another way to diagnose it
17 is they often have very very high levels of antibody
18 in the cerebrospinal fluid indicating that they're
19 making an immune response locally to the virus that's
20 present in the nervous system. Those are all the
21 kinds of things one looks for.

22 The imaging CTs or MRIs show big ventricles,
23 shrinking brain, basically.

24 Q Necrosis?

25 A Well, yes. You're getting cell death

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1 presumably due to the infection, the widespread
2 infection that's in the brain. So it's really quite a
3 characteristic picture which fortunately has
4 essentially disappeared from the U.S. with
5 immunization. We basically don't see this diseases
6 any more.

7 Q The course of the neurologic symptoms you're
8 talking about from the onset to the end point was
9 about a year?

10 A It's a year to two years. There are
11 occasional heroic medical care, et cetera. There are
12 occasional individuals who survive longer than that,
13 but that's the usual picture.

14 Q Does the condition ever not result in death?

15 A I don't know of any case reports where that
16 is the case, where there wasn't eventually death. As
17 you can imagine during the time, and there are many
18 parts of the world where this remains a very important
19 neurologic disease. Turkey happens to be a
20 particularly good example. They have clinicians who
21 are interested in studying it. So there have been a
22 lot of clinical trials to try to treat the disease
23 with riboviron or interferon or different things to
24 try to intervene, but these are all anecdotal case
25 reports, and since the duration of the disease is very

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1 variable, knowing whether your intervention actually
2 helped or not isn't clear.

3 There are certainly case reports that the
4 children did better for a while with these treatments.
5 I don't know of any cases of recovery where there
6 hasn't been some sort of antiviral treatment that is,
7 as I say, not recovery but improvement of some
8 variety. I think it's only ever occurred in the face
9 of some sort of antiviral intervention.

10 Q Recovery, was the recovery sufficient to --

11 A As I say, it's usually a slowing of the
12 downhill course is usually the kinds of things that
13 are being described. The person quit deteriorating as
14 fast as they had been before.

15 Q Pathologically, what's happening with the
16 cells here? What changes would we see at that level?

17 A As I mentioned, there's very widespread
18 infection, either when you do a biopsy because some of
19 these children do get diagnosed by brain biopsy.
20 Others you see an autopsy. But there's very
21 characteristic inclusion body formation that you see
22 in the infected cells in the nervous system. And as I
23 say, if you stain for virus antigens, it's everywhere.
24 This is not hard to find, let's put it that way.

25 Q When you do these biopsies have you seen any

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1 preferential effect of the measles virus on astrocytes
2 or microglia?

3 A It affects both neurons and the glial cells,
4 so both are affected. I think that most of the
5 deterioration is due to death of neurons. That's
6 what's really causing the neurologic deterioration.

7 Q It's actually cell death in neurons.

8 A Yes. I'm sure even the ones that are still
9 alive aren't functioning too well with all this
10 measles virus in them. You can stay alive and not do
11 so well.

12 Q You mentioned, what was SSPE and I don't
13 want to cut you short if there's anything more on
14 SSPE, but there was another instance of persistent
15 measles virus?

16 A The other places it can persist, and this
17 is, or the other situations in which it can persist.
18 So that's, as far as we know, are normal children that
19 have gotten measles and then get this very prolonged -
20 -

21 Q The wild measles?

22 A The wild measles, and then with SSPE.

23 There's another whole group of people who
24 get, again, mostly children, that can get measles and
25 develop a persistent infection. Those are children

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1 that are immune compromised. There are numerous
2 reports in the literature that immune compromised may
3 be because they have cancer, or because they have a
4 congenital immunodeficiency or because they have HIV
5 infection. There's a wide range of ways that you can
6 have an immunocompromised individual who then gets
7 measles.

8 When that happens, again, this is the
9 category of person that may not develop a rash, they
10 basically don't mount an adequate immune response
11 because it's usually, it's almost always children that
12 have a deficit in cellular immunity. They may have a
13 deficit in both cellular and humoral or antibody
14 immunity but usually it's cellular immunity. Those
15 children --

16 Q I'm sorry. What magnitude of immune
17 depression or suppression --

18 A This is profound. This is profound immune
19 depression.

20 As I say, somebody that might be on
21 chemotherapy or may have a lymphoma or have late stage
22 HIV infection. so this is pretty profound
23 immunosuppression.

24 Those individuals can develop progressive
25 measles virus disease which usually manifests itself

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1 within, usually within months. So the virus again
2 replicates relatively, or it causes its disease over
3 sort of a slow course, but it's a slow course over
4 months. So the most common presentation, they can
5 present either with neurologic disease and neurologic
6 deterioration, or with pulmonary disease and a giant
7 cell pneumonia, so respiratory problems. Those again
8 are progressive. Those all end in death and usually
9 appear, as I say within weeks to months after the
10 exposure to measles or the recognized exposure to
11 wild-type measles.

12 Q So this is much more rapid than SSPE?

13 A Oh, much. Much. Yes.

14 Q And you touched on the immune suppression
15 and the level of it, in this case do you see any
16 evidence, it's been postulated there's an immune
17 suppression. Do you see any evidence of immune
18 suppression of the nature that you're talking about in
19 these measles inclusion body cases?

20 A No. At least during the first year of life,
21 or whole history, there's really not been an increased
22 susceptibility to other infections. Usually these
23 children are susceptible to multiple infections. And
24 certainly the congenital immunodeficiency ones or the
25 HIV infected ones, have had other infections along the

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1 way. Measles, even measles vaccine is contraindicated
2 in a child with congenital immune suppression.

3 But I didn't see any evidence in her history
4 that she -- and she got some other live virus
5 vaccines. She got a polio vaccine, for instance. So
6 no indication that she had any problems with any of
7 those. In fact she mounted perfectly appropriate
8 immune responses to the vaccines that she received.

9 Q You mean these other ones?

10 A The other ones. If you looked at polio or
11 whatever.

12 Q Just to take a little aside here, you talked
13 about HIV. I think there's been some evidence
14 introduced about HIV patients who received measles
15 vaccine virus and how long it would take for them to
16 clear the measles vaccine virus. Are you familiar
17 with any of those studies?

18 A We've done a lot of studies on clearance,
19 per se, of the vaccine. We've done a lot of studies
20 on the induction of the immune responses to the
21 vaccine. I'm mixing up measles virus, the wild-type,
22 and vaccine.

23 If you talk about vaccine virus, there's at
24 least one case, and I'm sure there are, I know there's
25 more than one, but the one that alerted everybody was

GRIFFIN - DIRECT

1 a college student who actually got reimmunized with
2 measles vaccine at a time, and he was HIV infected.
3 This was before we the good antiretroviral therapy
4 that we have now. He basically had AIDS. He had a
5 very low CD4 T cell count. But it was almost a year,
6 during the subsequent year he developed progressive
7 respiratory symptoms and eventually died of a
8 pneumonitis and at autopsy it was due to measles
9 vaccine virus.

10 So over that year he was unable to clear the
11 virus that he was immunized with.

12 There are other cases of HIV infected
13 individuals who got the vaccine -- when they're very
14 profoundly immunosuppressed, that then developed a
15 progressive disease.

16 However, because wild-type measles is such a
17 severe disease in HIV infected children, it is
18 generally recommended that children receive the
19 measles virus vaccine even though they're HIV
20 infected. In Africa they give it even at a younger
21 age. They try to move the age down to six or nine
22 months, mainly because the immune suppression for HIV
23 is progressive over time. The thought is if you can
24 immunize them while their immune systems are still in
25 fairly good shape you'll get a good response to the

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1 vaccine and you won't get any complications.

2 Q In these individuals that you're talking
3 about, I understand the neurologic outcome was death
4 ultimately.

5 A Right. So was the respiratory outcome
6 usually.

7 Q Did you ever see a neurologic outcome of
8 autism in these cases?

9 A No, that's never been reported. And I
10 haven't seen it, no.

11 Q That's true either with the wild virus and
12 the vaccine virus?

13 A Right. No, autism was not a recognized
14 complication. There's neurologic complications, but
15 none of them are autism for wild-type virus.

16 Q Do you believe that in this case the MMR
17 vaccine more likely than not caused Michelle's autism?

18 A No. I think there's no evidence that it
19 did.

20 Q The pathogenesis that was proposed here that
21 measles vaccine virus persists, it replicates and
22 causes diseases in both the gut and the brain, is
23 there biologic plausibility to this pathogenesis
24 that's been laid out?

25 A I don't think so. I really do not see how

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1 you can put all this together. There's no evidence
2 that she has measles virus infection in the brain by
3 any of the criteria that we'd like to look at. First
4 of all, perfectly normal EEGs. An EEG shows slowing
5 which is not a characteristic feature of measles virus
6 infection of the brain, a normal imaging, not a
7 progressive neurologic disease, a pretty stable
8 deficit that's been there for --

9 Q Just to take a step back into something a
10 little more general. In general, a proposed
11 pathogenesis where measles vaccine virus persists,
12 this is the proposed pathogenesis. It persists, it
13 replicates, enters the brain, and causes autism. Do
14 you see biologic plausibility from what you understand
15 of measles virus, both vaccine or wild, for that
16 postulate?

17 A That is -- I mean --

18 Q Now causal autism we talked about --

19 A We know a lot about what measles virus does
20 when it gets in the brain and none of it is autism,
21 and none of the things we know about does she have.
22 So we know what measles virus looks like.

23 Q Taking a step back to this case with
24 something more general because the Court also needs to
25 have evidence here for something to apply to other

GRIFFIN - DIRECT

1 cases.

2 A Sure.

3 Q The basic pathogenesis that's postulated in
4 terms of vaccine virus causing measles that persist,
5 enters the brain, and causes autism. Do you see
6 biologic plausibility for that?

7 A I do not.

8 Q What's the worldwide mortality for measles
9 virus?

10 A It remains the second most common cause of
11 vaccine preventable death in children worldwide. It's
12 almost 500,000, 450,000 I think is the current
13 estimated numbers of deaths that are occurring
14 worldwide due to measles.

15 We forget in the U.S. what a serious disease
16 it was and why it was such an early target for the
17 development of a vaccine, because the morality is
18 substantial. And the mortality is substantial, even
19 in developed countries. It's less in developed
20 countries, but it's substantial. And if everybody
21 gets it, that's a lot.

22 Q Thank you.

23 MR. MATANOSKI: I have no further questions
24 at this time.

25 SPECIAL MASTER HASTINGS: Let me ask both

GRIFFIN - CROSS

1 counsel, is it your preference that we go ahead and
2 finish with Dr. Griffin tonight?

3 MR. MATANOSKI: It's certainly the
4 government's given Dr. Griffin's schedule.

5 SPECIAL MASTER HASTINGS: All right.

6 Ms. Chin-Caplan, do you want to go ahead?

7 MS. CHIN-CAPLAN: Sure.

8 CROSS-EXAMINATION

9 BY MS. CHIN-CAPLAN:

10 Q Good afternoon, Doctor.

11 A Hi.

12 Q Doctor, you have these slides that you
13 presented to the Court. Would it be fair to state
14 from the slides that you presented that the period of
15 maximum viremia coincides with the period of
16 immunosuppression?

17 A No. Immunosuppression lasts for a much
18 longer period. This little graph really only shows
19 the acute phase of measles. You can detect these
20 changes in immune responses, these increases of
21 susceptibility other infection during the acute phase,
22 but actually it continues for three or four months
23 after that.

24 Q My question was actually a little more basic
25 than that. From what we see on page four here, it

GRIFFIN - CROSS

1 seems that the period of maximum viremia which is
2 somewhere between I think it said 9 and 14 to 15 days,
3 is also the timeframe when one starts to see
4 immunosuppression?

5 A Yes, you may even be able to see it before
6 that.

7 Q It's just not clinically evident at that
8 time, correct?

9 A It can be. The time that children are
10 getting their secondary infections is often during
11 this period of the rash and shortly thereafter that
12 these complications of pneumonia and that sort of
13 thing occur.

14 As I say, it's a very paradoxical thing
15 because they're making a wonderful immune response to
16 measles and clearing of measles, but it's these other
17 infections that they're more susceptible to.

18 Q You indicated also that the period of
19 immunosuppression lasts longer than the period of
20 maximum viremia.

21 A In the wild-type disease it does. In
22 vaccine, as I say there's no immunosuppression really
23 in vaccine disease, but any immunologic abnormalities
24 that you can find are more confined, put it that way.

25 Q For the wild type, how long does the period

2800A

GRIFFIN - CROSS

1 of immunosuppression last?

2 A We've looked out, I guess it depends on how
3 you're going to actually define it, but there's
4 increased susceptibility to other infections certainly
5 for a couple of months after apparent recovery.

6 Q You indicate that increased susceptibility
7 for other infections were a couple of months after
8 what timeframe?

9 A After the clearance of the rash.

10 Q So roughly when the rash appears, about
11 seven days afterwards, the individual would still be
12 susceptible to infections for a period of two months
13 afterwards?

14 A Right Obviously it's varying from individual
15 to individual, but if you look at -- I think anybody
16 that's going to count measles and measles-related
17 deaths will often, which as I say are mostly due to
18 other infections, is usually in that two to three
19 month time period from the time of measles rash, or
20 recognition of measles.

21 Q Does the immune system still demonstrate
22 some sort of abnormalities when it's measured after
23 that timeframe?

24 A After the three months or so?

25 Q Yes.

GRIFFIN - CROSS

1 A We've not, I'm trying to think of what kinds
2 of studies. I suppose it depends on what you mean by
3 abnormalities. And if you're looking at skin test
4 responses, so a loss of the tuberculin response which
5 is common by the time of the rash. That takes about a
6 month before that comes back. Four to five weeks
7 before that's normal again.

8 So different parameters are going to be
9 different over different timeframes. As I say, we
10 mostly are concerned with this increased
11 susceptibility to other infections.

12 During all this normal, what was really a
13 normal immune response to measles, you have a lot of
14 changes in cells that are occurring and the kinds of
15 cytokines they're making, et cetera. Those things
16 gradually change over time.

17 We've certainly followed children out for
18 three months is usually about as long as you can
19 usually get parents to bring back children after
20 they've recovered from measles if you're going to do a
21 study. So you still may be able to find some
22 cytokines that are high at that point compared to
23 control children. So it's a gradual sort of going
24 back to what you might consider a baseline after
25 making this immune response.

GRIFFIN - CROSS

1 Q So there's a gradual return to baseline
2 after approximately three months, but you indicated
3 that you still see things like elevated cytokines
4 present for longer --

5 A In an occasional child you could. But three
6 months is sort of the outer limit. But I won't say
7 that if you looked at five or six -- Most studies stop
8 at a month, but we've carried studies out for three
9 months.

10 Q The elevated cytokines that you see, what
11 type of cytokines are they?

12 A We didn't really go into all these different
13 things that are happening with the immune system
14 during that period of time. But -- Can you put that
15 one back up? I guess you just need -- yes, that one.

16 If you look at the CD8 T cell response on
17 the bottom, that's a very up and down during the rash.
18 And again, all of this is looking at what's going on
19 in the blood because that's what we can sample.

20 So CD8 T cells are greatly expanded and then
21 they're quickly brought back. Those are the cells
22 that are probably most responsible for clearing the
23 virus in that top graph. They actually can kill cells
24 that have a virus infection. But if you look --

25 MR. MATANOSKI: This is Slide 4.

GRIFFIN - CROSS

1 THE WITNESS: Excuse me. Yes.

2 But CD4 cells have a much more complicated
3 role in -- I mean CD8 T cells also produce cytokines,
4 but CD4 cells have been most thoroughly studied and
5 their main job is to produce cytokines.

6 So early on during sort of that same time
7 you're seeing an elevated CD8 T cell response, you're
8 seeing what we call, and I know it's been discussed
9 here before, but a Type 1 CD-4, a T-Helper-1 type of
10 response and T-Helper-1 cytokines that are being
11 produced -- interferon gamma, IL2 are produced during
12 this acute phase.

13 Then those get, as I say, one of those
14 things that have to happen is you have to shut down
15 all of those cells so you can put things -- You have
16 to do two things. First of all, you want to mature
17 that antibody response, so that's another job of CD4 T
18 cells. The ones that are most important for producing
19 the cytokines that are most important for the antibody
20 response are the TH2 cells.

21 Those are producing cytokines like IL4,
22 IL13. There's another group of cells which are called
23 regulatory T cells which are probably the ones that
24 are helping to calm things down, bring things back
25 down more closer to baseline which produce IL10.

2804A

GRIFFIN - CROSS

1 We could measure, so those cytokines tend
2 to, there's a shift over to the TH2 type of an immune
3 response which makes an awful lot of sense. First of
4 all, you need to mature those B cells in the best
5 possible way for long term protection, and you also
6 need to dampen down that acute immune response. So
7 both the regulation and the B cell maturation are
8 things that are happening really after apparently
9 there is recovery from the infection. So it's all a
10 totally normal response to measles. But it involves
11 all these different normally produced cytokines.

12 Q So when the period of immunosuppression
13 begins, is there a skewing towards TH2?

14 A The immune suppression really start before
15 that, but it can still be present during that time,
16 and that skewing may have some role in the
17 immunosuppression. As I say, immunosuppression, a lot
18 of us have studied it and it's a very complicated
19 process. We don't fully understand it. But certainly
20 one of the jobs of the TH2 cytokines is to down-
21 regulate, macrophage activation, and down-regulate the
22 type 1 T cell response. That type 1 T cell response
23 may be important for another, if another virus came
24 along. That may be one of the reasons that there's an
25 increased susceptibility and it's certainly one of the

GRIFFIN - CROSS

1 hypotheses that we have out there. I don't think it's
2 the whole story. There are other hypotheses, that
3 there are just not enough cells, the cells get killed
4 off, that kind of thing, but those are pretty
5 transient.

6 Q When you have a TH2 skewing, is that an
7 indication that should the body encounter another
8 pathogen that it might not be able to clear it as
9 well?

10 A It's hard to know. It depends on what that
11 pathogen would be. As I say, we don't have a good
12 understanding of how much that TH2 response is
13 contributing to the immune suppression, per se, and
14 the increased susceptibility to other infections
15 versus just being totally a normal response.

16 Those studies are basically impossible to
17 do. There's no way to challenge somebody and do a
18 comparison of whether they got infected or didn't get
19 infected. Those were the kinds of studies that we
20 were doing in Peru, trying to look at children who got
21 pneumonia and other complications versus the
22 neurologic disease, versus they had no complications
23 at all. From this point of view they all looked the
24 same. That suggests that maybe there's something else
25 that is really accounting for that increased

GRIFFIN - CROSS

1 susceptibility to other infections, and it may be
2 something as simple as one of the places a virus
3 replicates is in the respiratory tract. If you have
4 damage to the respirator tract then, as I say
5 pneumonia is the most common complication, that you
6 fend off respiratory pathogens less effectively.

7 So I don't think we really have a good
8 understanding of how these various things relate. We
9 can describe what's there, but ascribing any one of
10 them to the actual increased susceptibility to other
11 infections is difficult.

12 Q Wouldn't it be fair to state that with TH2
13 skewing there's less TH1 to clear viral infections?

14 A TH1 cells are not what clear this virus
15 infection, and it doesn't mean that you can't induce
16 those TH1 cells if another virus infection comes
17 along. So measles induced is a perfectly good TH1
18 response, and then the later phase shifts, basically
19 the TH1 to TH2 shift occurs.

20 This may be common for many virus
21 infections. For whatever reason, people have really,
22 for acute virus infections people have really only
23 studied measles. That's probably because we're
24 studying measles.

25 We know that this increased substitutability

GRIFFIN - CROSS

1 to other infections occurs with a lot of other viral
2 infections. Chicken pox is a good example. Influenza
3 is another good example.

4 So there are lots of viral infections, but
5 the real complications are secondary infections, other
6 infections that occur, not the original infection. So
7 I think there's a lot of ways that a virus can make
8 you more susceptible to other infections and their may
9 be something common between them or they may be
10 different.

11 Q It's fairly well known that viruses can
12 cause immunosuppression and make people more
13 susceptible to opportunistic organisms, correct?

14 A Yes, some virus infections. It varies on
15 how important that is clinically, but wild-type
16 infections, I don't think there's any evidence for any
17 vaccines that that happens.

18 Q You edited the chapter on measles in "Fields
19 Virology" I think you said.

20 A I wrote it.

21 Q I'm sorry. You are the editor and you wrote
22 the chapter, correct?

23 A True.

24 Q Doctor, in that chapter you also included a
25 section on measles vaccine, didn't you?

GRIFFIN - CROSS

1 A I would hope so.

2 Q I'm looking at an exhibit in Dr. Fujinami's
3 which is Respondent's Exhibit R, Tab 17.

4 Doctor, it looks like Chapter 44 from
5 "Fields Virology," is that it? Measles Virus.

6 A I can't see it.

7 (Pause.)

8 A Right, but I don't know if this is the
9 current edition or not.

10 SPECIAL MASTER HASTINGS: Ms. Chin-Caplan,
11 did you say Tab 17 to Dr. Fujinami's?

12 MS. CHIN-CAPLAN: Eighteen.

13 BY MS. CHIN-CAPLAN:

14 Q Doctor, you have a section on attenuated
15 live virus vaccine.

16 MS. CHIN-CAPLAN: You don't have it for the
17 Doctor, do you?

18 MR. MATANOSKI: No. We don't have a copy.

19 (Pause.)

20 THE WITNESS: 1427 is in the references, is
21 that correct?

22 BY MS. CHIN-CAPLAN:

23 Q It's the page I have here. It says
24 attenuated live virus vaccines on the left hand
25 column.

GRIFFIN - CROSS

1 SPECIAL MASTER HASTINGS: Can you speak up?

2 THE WITNESS: I cant' read it.

3 BY MS. CHIN-CAPLAN:

4 Q It says attenuated live virus vaccine --

5 A I can't read it.

6 Q Okay.

7 Doctor, I'm going to refer you over to the
8 right-hand column, and the next to the last paragraph.
9 It says "Administration of standard dosage of live
10 attenuated measles virus vaccine results in transient
11 lymphopenia." What does that mean?

12 A That means a decrease in the number of
13 lymphocytes that are circulating.

14 Q Would that affect ones ability to fight off
15 infection?

16 A Not that we recognize.

17 Q So clinically you're saying it doesn't
18 appear to cause any harm.

19 A There is absolutely no evidence that it does
20 clinically. We can measure a number of changes. And
21 a lymphopenia is probably due, at least our
22 understanding of that, is probably due to change in
23 circulation of the cells because as I say, all of this
24 induction of the immune response is going on in the
25 lymph nodes. The cells that are running around in the

2810A

GRIFFIN - CROSS

1 blood, which is what you're measuring for lymphopenia
2 are not useful from that point of view until they get
3 their instructions and get expanded in the lymph
4 nodes. Then they come back out.

5 So during the time of the induction of the
6 immune response, and this happened within wild-type
7 measles as well, it was much more profound than it is
8 in vaccine. You see the transient dip which is
9 probably due to the cells getting the signal that the
10 best place to be is in the lymphoid tissue
11 participating in the induction of the immune response,
12 and then they come back out.

13 I think it's most likely this is a
14 trafficking, it's not a real change in the number of
15 lymphocytes, there's a change of where they are at any
16 one time.

17 Q Would that be the same thing for wild-type?

18 A For the wild-type, as I say, it's a much
19 more profound change that occurs really during that
20 rash phase. Again, during that immune response,
21 intense immune response phase. So it's one of the
22 things that's happening during the immune response.

23 Q It's an attenuated version of what would
24 occur in wild-type, is that it?

25 A This lymphopenia?

2811A

GRIFFIN - CROSS

1 Q Yes.

2 A Yes.

3 Q The suppression of delay type hypersensitive
4 skin test responses to recall antigens, what exactly
5 does that mean?

6 A Those are the tuberculin tests for the most
7 part. Those have been documented to be decreased --
8 Mostly those papers are fairly, were with the original
9 vaccine. It went through a stage of the original
10 vaccine and then a more attenuated version, which is
11 our current strain, Moraten, that causes less of that.
12 I'd have to see what the references actually are, but
13 a lot of them are early vaccine references. But there
14 was that documentation.

15 Q When it says that you lose the tuberculin
16 test result, is that it?

17 A Yes, you can. Again, it's not clear that
18 that happens with the current vaccine. Put it that
19 way.

20 Q But in the earlier vaccines it was --

21 A Attenuated vaccine, right.

22 Q This altered cytokine production. Are these
23 the cytokines that you were referring to earlier? The
24 IL4?

25 A Yes. And again, those are seen, I think

GRIFFIN - CROSS

1 studies have been done more and more. You see those
2 mainly, in fact if you look at a number of our
3 publications, we're looking at individuals who are
4 being revaccinated. So right now we give two doses of
5 the vaccine. In outbreak situations like occurred in
6 '89, '91, we gave a second dose, we sort of
7 reimmunized all the people working in the hospital,
8 for instance, because of the outbreak.

9 I don't know why this is. I assume it's
10 because you're inducing that memory response that you
11 see actually more of these cytokines that were sort of
12 like what you could see in wild-type. So you see the
13 IL4, et cetera. You can see those induced as a part
14 of the memory response. Again, it's a manifestation
15 of the fact that the T cells are there, the memory T
16 cells are there. They've helped the B cells and the
17 kind of memory T cells that you have are those same
18 variety that were induced during the acute response.

19 The basic immune response, just as a matter
20 of greatly attenuated degree. I mean the amount of
21 antibody you get in response to vaccine is about ten-
22 fold lower than you get in response to wild-type
23 infections. So there's a lot of matter of degree
24 here. It all adds up to it's not a clinically
25 relevant, but you can definitely identify changes that

2813A

GRIFFIN - CROSS

1 are occurring as a part of the induction of the immune
2 response to the vaccine.

3 Q And the changes that were listed in your
4 chapter here, they're the same changes that you see in
5 wild-type except to a lesser degree. Is that what
6 you're saying?

7 A Fundamentally. We've only looked at a few
8 cytokines. In fact we haven't looked at IL10 really
9 at all, which we've looked at in wild-type disease.
10 But certainly if you look at the sort of
11 characteristic, interferon gamma IL4, yes, they are
12 similar.

13 Q And interferon gamma is a TH1 response,
14 correct?

15 A And a CD8 response.

16 Q You need interferon gamma to clear
17 infection, correct?

18 A Not necessarily. You need to be able to
19 induce -- infections vary. What you require. It's
20 one thing to say the memory response to measles is IL4
21 and not interferon gamma. It's a totally different
22 thing than saying what's the response to a new virus
23 where you're going to go through this whole scheme
24 again, to induce the CD8, the CD4, to this new batch
25 of antigens and virus antigens and that sort of thing.

2813B

GRIFFIN - CROSS

1 There's no reason to think that's not going to happen

2814A

GRIFFIN - CROSS

1 in a perfectly normal way even though the memory
2 response to measles, per se, is still that memory
3 response to measles.

4 Q And you in fact have actually done some
5 cytokine work with Dr. Ward, correct?

6 A Right.

7 Q That was you measured IL4 after vaccine?

8 A Those were in the hospital workers who were
9 being revaccinated. So as I said, we were really
10 looking at the memory response.

11 We've done studies subsequently in babies
12 who are being, not with Brian, but I've done some
13 studies subsequently in babies that are being
14 immunized with MMR or with just measles alone, and we
15 really can't find those changes in the primary
16 response. So they may just be much easier to see as a
17 recall response.

18 Q So is it the opinion now that you only see
19 it as a secondary response in somebody that's already
20 been exposed previously?

21 A It's certainly more profound. It's a
22 different sort of memory response, it's more easily
23 seen for a memory response probably because you
24 already have a fair number of those cells than it is
25 in the primary response. But as I say, I still think

GRIFFIN - CROSS

1 the same thing in miniature is going on in the primary
2 response. But since we can only measure what's going
3 on in the blood, and when you're talking about
4 immunizing infants and studying them you're very
5 restricted in the number of cells, how often you can
6 actually look at the responses, et cetera. So those
7 studies are just much harder to do and most people
8 haven't done them.

9 Q When you did your IL4 study with Dr. Ward,
10 you indicated it was in hospital workers, correct?

11 A Yes.

12 Q You only went out about 14 days after the
13 immunization? Is that it?

14 A I think so. I'd have to relook at the paper
15 to, but yes. I don't remember how long we went out.

16 Q It wasn't a long-term follow-up.

17 A No. It may have been three weeks, but --

18 Q Okay.

19 Doctor, we had talked earlier about your
20 Slide 4, and you know that Michelle Cedillo had a
21 temperature of 105, almost 106 at approximately seven
22 days out after measles immunization. If one looks at
23 your chart that seems to coincide with the period of
24 maximum viremia.

25 A I think she had a rash at the same time,

2816A

GRIFFIN - CROSS

1 didn't she?

2 Q I don't recall. I remember the fever.

3 A Okay.

4 Q But the fever would be occurring at the time
5 of maximum viremia, wouldn't it?

6 A I don't know if it's going to be, or maximum
7 immune response.

8 Q Maximum immune response. Okay.

9 A But the immune response is being induced in
10 response to the virus. These things, as you can see
11 from this chart, are all happening at the same time.

12 Q Yes. So would it be fair to state that the
13 fever was probably related to her MMR?

14 A I think it probably was, yes.

15 Q We do know that that fever subsided for a
16 period and it recurred. It recurred at approximately
17 16 days out. She had the fever for about four days,
18 then it went away for a few days then it came back.
19 Do you believe that second fever is also related to
20 the MMR?

21 A I would doubt that. Children get fevers due
22 to a lot of different things especially at that age.
23 I would not think that was, a biphasic response, is
24 not seen as far as I know, with measles vaccine or
25 with measles.

2816B

GRIFFIN - CROSS

1 Q But that would still be within the period of

GRIFFIN - CROSS

1 immunosuppression that you've documented --

2 A But right here you're looking at wild-type
3 virus. You're not looking at vaccine. And there's
4 one major difference is that you get a very small
5 amount, for wild-type virus you get a very small
6 amount of virus that you breathe in, and then it takes
7 all those days of seven, eight, nine, ten days to
8 build up to the amount of virus and induce the immune
9 response, et cetera.

10 With a vaccine virus you're inoculating a
11 fairly, thousand plaque forming units, infectious
12 units, subcutaneously, so you're bypassing all that
13 early stage.

14 I'm just saying the vaccine response is
15 earlier. It's skewed, so to speak, to be earlier than
16 you
17 see with wild-type virus where you have to go through
18 a phase of a lot of virus replication to even get to
19 the point that you have as much virus as you put in
20 for the vaccine to induce the immune response, and you
21 have to do that with a vaccine because it's not going
22 to replicate as well, you need to sort of get a head
23 start.

24 So I think for the vaccine usually it's
25 around seven to ten days, five to ten days is the

2818A

GRIFFIN - CROSS

1 usual time period that you see the complications, the
2 rash, fever, et cetera, due to the vaccine, and those
3 have been pretty well studied.

4 I think 16 days would be quite a ways out
5 from what the observed, or what I would expect with
6 the vaccine virus causing a fever per se.

7 Q Do you know whether IOM has indicated that
8 reactions occurring from 5 to 15 days would be
9 considered to be related to the measles?

10 A Usually they give a fairly broad range. So
11 16 days is outside their 15 days, but --

12 Q If they say 15 days and it occurred at 16
13 days, you really wouldn't quibble that much about the
14 day, would you?

15 A I don't know. I just think that this
16 biphasic, the fact that she already had something that
17 makes sense that it was related to measles vaccine
18 would suggest that the second fever was due to
19 something else.

20 Q There was also testimony that Michelle
21 suffered diarrhea about two weeks after the
22 immunization. In your opinion, would that be related
23 to the MMR?

24 A I wouldn't know any reason to think it was.
25 As I say, there's been lots of pretty extensive

2819A

GRIFFIN - CROSS

1 studies looking for any kind of infectious
2 complications that occur as a consequence of
3 vaccination, of MMR specifically. I have no way to
4 know. I don't know how much she was worked up or
5 people tried to figure that out, or if she was even
6 seen.

7 Q So when they say that measles is
8 enterotropic, what exactly does that mean?

9 A I wouldn't say measles was enterotropic.

10 Q No?

11 A No. Measles is lymphotropic. It replicates
12 again, it replicates in lymphoid tissue everywhere.
13 It's in the appendix, it's in the spleen, it's in the
14 lymph nodes, it's in the tonsils, it's in the thymus.
15 You look at any lymphoid tissue and it's infected.

16 In addition to that it can be found in a lot
17 of other, and a lot of gut lymphoid tissue. As I say,
18 the appendix is a well recognized site for it to
19 replicate and I'm sure it probably replicates in the
20 other lymphoid tissue as well.

21 But it doesn't have any special predilection
22 to replicate in the gut or certainly the gut mucosa.
23 In contrast to an enterovirus or something where
24 that's the main site of the virus replication.

25 Q But it's definitely neurotropic, correct?

GRIFFIN - CROSS

1 A It's neurotropic not in this type of sense.
2 It can cause neurologic disease that we've already
3 talked about which are very characteristic diseases,
4 SSPE, measles inclusion-body encephalitis where again
5 you see the same kind of pathologic picture and a very
6 characteristic clinical picture. So there's no doubt
7 in those special situations of where you have this
8 infection at a very early age that then leads to this
9 SSPE 7 to 10 years later, or this infection in the
10 face of profound immunosuppression, frankly, that it
11 can get into the nervous system. That's true.

12 It's interesting that the virus that's
13 present in the nervous system is quite heavily mutated
14 compared to the original virus. So it sounds like, it
15 looks like, and again we don't have any way to really
16 do these studies, but it looks like for the virus to
17 be able to be in the nervous system requires these
18 mutations and these mutations actually alter the
19 ability of the immune system to see the virus.

20 Q Would you say that for a virus to persist
21 that there has to be some sort of immune dysfunction?

22 A Oh, no. There's lots of viruses that
23 persist when they infect people that are originally
24 perfectly normal. I mean HIV is a perfect example.
25 You have Hepatitis C virus. All the herpes viruses

2821A

GRIFFIN - CROSS

1 that persist in most of us after, and we're hopefully
2 immunologically normal. So virus persistence is
3 certainly not cause, it doesn't mean you have to be
4 immunosuppressed to have virus persistence.

5 Q But if a person is immunosuppressed the risk
6 for viral persistence increases, doesn't it?

7 A Yes, I mean I guess it depends on the kind
8 of immunosuppression. We know that people who are
9 hypogammaglobulinemic, for instance, don't have good
10 antibody responses, actually do pretty well with
11 measles, interestingly enough, but they do badly with
12 polio or some of the other enteroviruses. They do
13 very badly with certain bacteria which really requires
14 antibodies. And while there are other diseases where
15 components of the cellular immune response is much
16 more important for virus clearance and some where the
17 antibody response is the most important. Even some
18 aspects of the innate immune response are important
19 for clearance of herpes viruses. So all these viruses
20 are very, they're wily, they're complicated, and their
21 interactions with the host are complicated. So you
22 can't extrapolate from one to the other very easily.
23 You have to study each one and understand it.

24 Q And measles is particularly difficult to
25 study as you indicate because it doesn't really occur

GRIFFIN - CROSS

1 in little rodents, correct?

2 A It's a human virus, yes, but there's been a
3 lot of human studies and there have been a lot of
4 monkey studies that are going on. so you can do it.
5 It's not as easy as infecting a mouse, that's true.
6 It also may not be as relevant.

7 Q You have to use monkeys primarily to study
8 the measles virus, don't you?

9 A We do a lot of human studies, too. We study
10 both people and monkeys.

11 Q But if you wanted to see viral persistence,
12 you would probably test it in a monkey as opposed to a
13 human?

14 A Well, we've done a couple of studies in
15 Zambian children following virus clearance. I think
16 it's really a question, if you look on the top of the
17 graph, that curve represents ability to recover
18 infectious virus. So if you try to grow virus, that's
19 what that curve looks like.

20 However, if you do PCR on those same
21 individuals in that graph, you can find virus for a
22 much longer period of time by RT-PCR. it's much more
23 sensitive. It takes a while to get rid of all of the
24 cells that were ever infected. There's no longer any
25 spread of the virus. But the process of virus

2823A

GRIFFIN - CROSS

1 clearance as we have more and more sensitive
2 techniques, it's not as straightforward as most people
3 would hope I guess. The dogma is that, that curve is
4 the dogma that once you get that infectious virus
5 you're not going to be able to, that all the virus is
6 gone. But we know from studies, a number of different
7 kinds of studies, that if you do RT-PCR on, it can be
8 urine or nasopharyngeal swabs, or blood in children
9 who have recovered from measles, or monkeys, and we've
10 done it on both monkeys and kids, then it takes
11 actually, well in kids we can still find it at three
12 months. Probably in monkeys we saw it out to six
13 months. So by five to six months, all the virus is
14 gone. But as I say, it just depends on the
15 sensitivity of the technique that you apply to trying
16 to -- Which is probably the reason, the fact that it's
17 clearance is a prolonged process, it takes a while in
18 wild-type infections, that you continue to see the
19 cytokines and the T cell responses, et cetera, for a
20 period of time after the rash is gone.

21 As I say, when the rash is gone, the fever's
22 gone, the kid feels fine, but a lot of other things
23 are still going on with the immune system after that.

24 Q You've done studies on viral persistence,
25 haven't you?

GRIFFIN - CROSS

1 A Yes.

2 Q You've indicated that if you used more
3 sensitive techniques that you could find viral
4 persistence for a long period of time and it depends
5 on the type of techniques that you use, correct?

6 A Yes.

7 Q You've actually done some experiments on, is
8 it Sindbis virus?

9 A Sindbis virus, yes.

10 Q Yes. And I think there's an article you
11 attached at Respondent's Exhibit V, Tab 64. The title
12 of this is "Long-Term Intraparenchymal Ig Secretion
13 After Acute Viral Encephalitis in Mice."

14 Doctor, I'm going to have your counsel --

15 A I know the study well.

16 (Laughter.)

17 Q It's been a while.

18 A We're still working on this question.

19 Q You used PCR technique to detect Sindbis
20 virus RNA in the brain, is that true?

21 A Yes.

22 Q And it indicates in the abstract that three
23 months after inoculation 47 percent of the B cells
24 found in brains are secreting antibody specific for
25 Sindbis virus structural protein. Is that true?

2825A

GRIFFIN - CROSS

1 A It's true.

2 Q By a year, 62 percent are Sindbis virus
3 specific. B cells secreting IgG2A predominant.

4 So even after a year there's still RNA
5 present.

6 Further on it says, "Polymerase chain
7 reaction data indicate that despite complete clearance
8 of infectious virus by seven days, Sindbis virus RNA
9 is still present in brain at least six months after
10 infection."

11 A Right. In fact this study, and this is the
12 other kind of virus that we've studied, so this is a
13 virus that infects neurons. That's its main target
14 cells, the way we do these studies, was, and we were
15 very interested as I already indicated, one of our
16 research interests gives virus clearance. And what
17 does the immune system have to do to actually clear
18 virus?

19 So in this case this virus infects neurons.
20 Neurons are not a population of cells that one can
21 replenish. You lose your neuron, your neuron's gone,
22 you're not going to get a new one. But it's a type of
23 viral encephalitis that these mice can recover from.
24 So you can get acute virus replication that's similar
25 to what I've just shown you from measles, and then you

2826A

GRIFFIN - CROSS

1 can't get infectious virus back any more, which
2 frankly is due primarily to the fact that you've got a
3 lot of antibody around, but the mice totally recover.

4 This is true of humans, too. You can have a
5 viral encephalitis that people get better from totally
6 where they have infected neurons and they don't have
7 long term paralysis or mental retardation or anything
8 else.

9 In this series of studies that we continue
10 to do on this particular virus that's neuronotropic
11 and affects neurons primarily, what became clear was
12 that the immune response had a noncytologic approach
13 to clearing the virus. So basically to clear all the
14 infectious virus you had a, if you look by PCR, you
15 found a dramatic decrease in the amount of RNA that
16 was present, but it never totally went away. That's
17 because neurons are very special cells. They're cells
18 that don't turn over. As I say, the neurons you get
19 when you're born are pretty much the neurons you're
20 going to have.

21 Basically what this specialized group of
22 cells, and it's true probably of cardiac cells as
23 well, myocytes who don't replace those very well. The
24 best way for the immune system to get rid of a virus
25 is to kill the cell that the virus is in. And if it's

2827A

GRIFFIN - CROSS

1 disadvantageous to kill the cell the virus is in, like
2 it's a neuron, then it is very smart for the immune
3 system to figure out another way to be able to control
4 the virus without having to actually kill the cell and
5 get rid of it.

6 That's what happens. It's sort of peculiar
7 to long-lived cells that can't be replaced. Cells
8 that turn over, so like cells in most of our body and
9 that's certainly true of epithelial cells in the lung
10 or the gut, lymphocytes, all those cells, those
11 populations turn over pretty rapidly. It maybe a
12 month or two months or something like that, but they
13 eventually, there's new ones. You don't have long-
14 lived cells for the most part. Your gastrointestinal
15 epithelial cells are turning over all the time.

16 If that's where the infection occurs, then
17 fine, kill off the cells. We'll make new ones.

18 So if you think about influenza, I always
19 think of as a good example, because that's what
20 happens with influenza. You've had influenza, you
21 know the cough can persist for a couple or three
22 weeks, and that's because it's taking that long to get
23 all your new cells growing back and repopulating your
24 respiratory tract.

25 So the cells that we know that measles virus

GRIFFIN - CROSS

1 infects are all cells that turn over. And so it's
2 certainly true in the gut. A classic example of
3 pretty rapid turnover of cells.

4 So there isn't this long-lived cell
5 mechanism or problem with measles, and we think most
6 of the clearance is occurring due to cytotoxic T
7 cells, basically, that are actually killing the cells.
8 In many instances the virus infection itself will kill
9 the cell, which is actually a handy dandy way to get
10 rid of an infected cell if the immune system doesn't
11 do it. If that cell dies, even if it's just dying as
12 a part of its normal life span, it normally only lives
13 a couple of months that those cells turn over. So
14 they may be an important component of clearance of
15 some viruses. So the nervous system is a very special
16 example and as I say, I think it's a fascinating
17 biologic problem as to how you control viruses in a
18 cell that you can't afford to get rid of. So that's a
19 reason we're doing those studies. And we have a fair
20 amount of data on how the immune system is doing that.
21 But I don't think it's relevant to measles, frankly.

22 Q Doctor, in this article, in the abstract,
23 the very last sentence says, "The persistence of
24 Sindbis virus RNA suggests that viral protein may
25 continue to be made providing the impetus for the

GRIFFIN - CROSS

1 continued presence of Sindbis virus specific B cells
2 in the brain."

3 A Uh huh.

4 Q In this sentence you're indicating that
5 because you're able to find the RNA that it's --

6 A No, it's not because of the RNA. It's
7 because we're finding the B cells.

8 Q The antibodies.

9 A The B cells in the nervous system. so these
10 are B cells that have gone specifically, so we're
11 looking at B cells in the nervous system. This is not
12 a place B cells normally are, and they're there making
13 antibodies. And so the reasoning there is that the B
14 cells need to be in the place where the viral protein,
15 where the virus is, and that they need to, and that
16 they need to be stimulated by something. Why would
17 they go there and why would they stay there if there
18 wasn't some stimulus for them to keep making the
19 antibody in the nervous system?

20 The same kind of thing happens in SSPE. It
21 turns out it's not very effective. As I mentioned
22 before, one of the ways that you diagnose SSPE is to
23 look for increased levels of antibody in the CSF.
24 That's because B cells have come into the brain in
25 response to that infection that's there and those

2830A

GRIFFIN - CROSS

1 proteins that are being made and are easily detected
2 by immunocytochemical staining or whatever you want to
3 look at. You can find a protein in the brain.

4 So I think that the B cells are there, the
5 reason we think the protein is there is because the B
6 cells are there. But the RNA itself would not give us
7 any information on whether proteins were being made.

8 Q Doctor, as I read this it seems like the
9 persistence of the RNA suggest that viral protein will
10 continue to be made providing the impetus but the
11 continued presence of Sindbis virus specific B cells
12 in the brain. So it's the presence of the RNA that
13 generates the antibody response, is that what you're
14 saying?

15 A No, the antibody response is not to the RNA.
16 The antibody response is to the proteins.

17 Q Right, but that's what you said.

18 A You need RNA to make protein.

19 Q "The Sindbis virus RNA suggests that viral
20 protein may continue to be made."

21 A Right, because you can't make protein
22 without RNA.

23 Q Right. So the presence of the RNA you said
24 suggests that the viral protein is being made.

25 A It's the presence of the B cells. You have

GRIFFIN - CROSS

1 to have RNA to make protein, and you'll not get B
2 cells, but RNA does not have to make protein. RNA can
3 make protein or not, depending on what it's doing or
4 what kind of RNA it is. But the B cells can only see
5 the protein. So our clue to the fact that the RNA was
6 coding for protein to be made was the fact that B
7 cells were there. You need all three components.

8 Q Okay. Understood. Doctor, in your opinion,
9 I'll ask that counsel give you a copy of your opinion.

10 A I have a copy of my opinion.

11 Q Okay. I just wanted to go through some of
12 this with you. You drafted this opinion before Dr.
13 Bustin was a witness.

14 A Right.

15 A You had participated in the U.K. litigation
16 is that true?

17 A Yes.

18 Q What was your role in the U.K. litigation?

19 A Well, similar to here. An expert on measles
20 and immune responses to measles.

21 Q What knowledge did you have of the
22 laboratory procedures in the O'Leary laboratory?

23 A I think most of it's privileged information.
24 He may have to advise me. I have a lot of information
25 that came out as a part of that case, much of which is

2832A

GRIFFIN - CROSS

1 not public so I don't know what I can tell you.

2 MR. MATANOSKI: I don't actually think that
3 she would be cleared to talk about what knowledge she
4 would have on the case, Your Honor. Obviously it was
5 Dr. Bustin and Dr. Simmons and Dr. Rima whose reports
6 we obtained.

7 THE WITNESS: I mean I have those reports
8 and I know what they said, but --

9 SPECIAL MASTER HASTINGS: Let her ask the
10 question.

11 MR. MATANOSKI: I think if you want to ask
12 whether what she put in here is dependent on anything
13 she knew from that litigation, I think she could
14 answer that.

15 MS. CHIN-CAPLAN: And that's exactly what --

16 BY MS. CHIN-CAPLAN:

17 Q I wanted to know where the basis of your
18 opinion for, for your criticism of the O'Leary lab
19 comes from.

20 A I have to see what I actually said here. A
21 lot of it comes from the literature. There's been a
22 lot of public criticism. There have been retractions
23 by the people that published the paper, the Uhlmann
24 paper. Most of those authors have disavowed those
25 conclusions. There's been, actually very early on in

GRIFFIN - CROSS

1 the Wakefield stuff I actually visited the U.K. at his
2 invitation to be a consultant and it was rapidly
3 apparent to me they didn't know how to do PCR. They
4 were in sort of a phase, I think it was before the
5 O'Leary thing. But I was suspicious from just the
6 personal interaction.

7 But I think that most of what is in here is
8 not from what I learned in the U.K.

9 Q So the basis for your opinion that, and I'm
10 looking at page eight of your report.

11 A I didn't number my version here. Okay.

12 Q You speak of, in the middle of that first
13 paragraph, "any negative for controls was accepted as
14 the result and any positive for patients was accepted
15 as a result, even if other assay runs on the same
16 patient population are giving the opposite result."

17 Are you referring to a different paper? Are
18 you referring to --

19 A I'm referring to this example that I gave
20 about the HTLV-1 paper which happened to be a paper I
21 reviewed and tried to prevent being published. So I
22 had a fair amount of knowledge about what the problems
23 were with that paper and it was just a very, and the
24 literature is full of false PCR data. This is just
25 one I happened to know a fair amount about.

2834A

GRIFFIN - CROSS

1 Q Okay.

2 SPECIAL MASTER HASTINGS: Doctor, she asked
3 you, we'll get through this quicker. I think she
4 asked you a very simple question. What paper you were
5 referring to. And now you're telling us about the
6 paper. I think the answer to the question, you
7 answered it already.

8 THE WITNESS: Okay.

9 BY MS. CHIN-CAPLAN:

10 Q Doctor, that next sentence, you say most of
11 these points apply to the way in which the study by
12 Uhlmann, et al was carried out. What points are you
13 referring to?

14 A I haven't been able to find your spot.
15 I think it was whether the controls were
16 being done appropriately.

17 Q The control?

18 A Right.

19 Q That was in the Uhlmann paper?

20 A Right.

21 Q Anything else?

22 A I certainly had talked to Afzal, these
23 people in the U.K., people who had tried to, I'm
24 trying to find this.

25 The sequencing, there was no evidence of

2835A

GRIFFIN - CROSS

1 sequencing of the PCR product which was necessary. So
2 those kinds of things were done in this HTLV paper and
3 also were apparent that it was a problem in the
4 Uhlmann paper. I did not base this on knowing all the
5 things in the Bustin report because I did not know
6 those things.

7 Q Okay. Doctor, I'm just going to ask you
8 because it's not clear to me when you refer to the
9 problems of controls and the sequencing in the Uhlmann
10 paper. If you would just look at Tab 66, Exhibit 66
11 in your report, attached to your report, can you tell
12 me what is the problem with the control?

13 A I'm not going to be able to give you a
14 detailed critique of the Uhlmann paper, if that's what
15 you're looking for.

16 SPECIAL MASTER HASTINGS: Which tab was it?

17 Q 66.

18 A I don't know what that is.

19 Q So you can't tell me what the problems with
20 the controls were in the Uhlmann paper?

21 A It was, unfortunately I don't have the
22 Uhlmann paper in front of me.

23 (Pause.)

24 A The biggest problem was they didn't do
25 sequencing of their product.

2835B

GRIFFIN - CROSS

1

I don't want to claim to be a PCR expert.

GRIFFIN - CROSS

1 We do PCR. We use a lot of controls.

2 Q It was the sequencing that you --

3 A That's the biggest thing, in my opinion.

4 It's the only way you can detect whether you have
5 contamination, the only way you can detect that you
6 have vaccine virus versus wild-type virus. It's just
7 a necessary part of this kind of analysis.

8 Q So it's really that last step, that
9 sequencing that you objected to the fact that it
10 wasn't done in the paper.

11 A Right.

12 Q Doctor, you mentioned Dr. Afzal, you
13 discussed something with Dr. Afzal. What --

14 A I knew he was doing this study of comparing
15 labs.

16 Q Comparing labs?

17 A Yes.

18 Q So Doctor, would that be --

19 A And the O'Leary lab didn't participate in
20 that.

21 Q Right. But there were other labs that
22 didn't participate, isn't that true?

23 A That did not?

24 Q Yes.

25 A Yes, but none of those were putting out a

2837A

GRIFFIN - CROSS

1 diagnostic test for measles for autism.

2 Q Well Doctor, how many labs were invited to
3 participate?

4 A I'm sure that probably every lab that had
5 ever published on PCR and measles probably was invited
6 to participate.

7 Q If I told you that there were 13 that were
8 invited to participate, would that sound about right?

9 A Probably.

10 Q If I told you that six decided not to join
11 into the study, would that sound about right?

12 A I can't remember how many.

13 Q Approximately half decided not to
14 participate.

15 A Right.

16 Q Doctor, if I told you that the problem when
17 comparing these laboratories, there was a thousand-
18 fold difference between the laboratories and their
19 results, isn't that true?

20 A I don't remember the specifics of the paper.
21 There was a difference. There was one laboratory
22 actually that stood out as I recall as being
23 particularly problematic compared to all the others.

24 Q And there was a thousand-fold difference in
25 sensitivity.

2838A

GRIFFIN - CROSS

1 A I don't remember.

2 Q So if I told you that, you wouldn't dispute
3 that.

4 And if I told you also that the one lab for
5 which there appeared to be some cross contamination
6 which was FDA, that wouldn't, you wouldn't --

7 A The lab that I remember had the biggest
8 problem was the Japanese lab.

9 Q The Kawashima one?

10 A It was something --

11 Q And Doctor, if you look on page 175 of Tab 1
12 of your report, approximately 11 lines down. The
13 sentence says, "Although none of the participating
14 laboratories reported the presence of measles virus
15 nucleic acid in any of the gut samples A through D
16 that were derived from four new cases of Crohn's
17 disease, Laboratory 5 described an ambiguous result
18 from one of these samples. It is reasonable to
19 speculate that the measles virus signal observed in
20 Sample A originated through cross-contamination."

21 Laboratory 5 is FDA.

22 A Okay. That's the way we figure out cross-
23 contamination.

24 Q Okay. Now you also mention in your report
25 that people attempted to replicate Dr. O'Leary's

2839A

GRIFFIN - CROSS

1 results and were unsuccessful, and you cited Afzal and
2 D'Souza.

3 A Uh huh.

4 Q Doctor, Afzal and D'Souza were tests that
5 were done on blood, is that correct?

6 A Yes.

7 Q Mononuclear cells.

8 A Uh huh.

9 Q and they were unable to recover any measles
10 RNA is that true?

11 A Right.

12 Q And Doctor, we do know that the measles RNA
13 in this case was recovered from gut tissue, is that
14 true?

15 A If it was recovered.

16 Q And if it was recovered do we know what the
17 correlation is between the gut tissue and the
18 mononuclear sites?

19 A I don't think that, for PCR results I'm not
20 sure that is relevant. Cells are cells. It depends on
21 what you're trying to deduce from it. But for the
22 purposes of how you do PCR and how you detect
23 positives, you do it the same for one sample versus
24 another.

25 Q Wouldn't it be important to try and limit

2840A

GRIFFIN - CROSS

1 the variability as much as possible?

2 A I don't know, it depends on -- I think PBMCs
3 are probably pretty good at limiting the variability.
4 There are ongoing studies to actually try to look at
5 gut tissue, but there's a lot of problems with
6 biopsying children who don't need to be biopsied, and
7 just to do PCR on their gut tissue.

8 Q Doctor, don't you think these symptoms that
9 these kids are having are real?

10 A Oh, I don't doubt that they have symptoms,
11 but there's a lot of reasons to have symptoms, and
12 none of them that I can think of would be measles.

13 Q When they have symptoms it's reasonable to
14 work up the symptoms, isn't that true?

15 A Well, yes. If you think this is medically
16 indicated and that you're going to learn something
17 that you're going to be able to do something about by
18 doing that medical procedure, then I guess biopsy is
19 appropriate. But I think that for many of these
20 children that's not thought to be the case.

21 But I'm not a pediatric gastroenterologist,
22 I'm not an expert on autistic enterocolitis or work up
23 these kinds of kids. I'm outside my territory if
24 you're asking me how you take care of these patients.

25 Q Doctor, when there's a wild measles

GRIFFIN - CROSS

1 infection you're able to recover that virus from the
2 blood for a period of about seven days after the wild
3 virus has appeared, is that true?

4 A There's a period of viremia, in wild-type
5 measles the viremia is generally about 9 to 14 days,
6 there's a period. And yes, it may be five to seven
7 days during which you could actually recover the
8 virus.

9 Q And you're not always able to recover the
10 virus, isn't that true?

11 A Well you can if you take it at the right
12 time.

13 Q If you take it at the right time. Right.
14 And even if you take it at the right time, not
15 everybody has been able to recover it, isn't that
16 true?

17 A I think it depends on what they're using for
18 their recovery technique. Most people don't try to
19 recover measles, frankly. It's not the way you
20 diagnose measles, it's a laboratory procedure, it's a
21 research thing basically to try to recover the virus.

22 If you culture cells on the first day of
23 rash appropriately I think most people can recover the
24 virus. It becomes steadily less likely with time.

25 Q Doctor, if you go to Tab 48 of your exhibit,

2842A

GRIFFIN - CROSS

1 on page two, this is Detection of Measles Virus Genome
2 Directly From Clinical Samples By Reverse
3 Transcriptive Polymerase Chain Reaction and Genetic
4 Barrier ability.

5 Under the introduction it's talking about
6 recovering measles virus. Is that true?

7 A In the abstract or --

8 Q I'm in the introduction.

9 SPECIAL MASTER HASTINGS: Page two.

10 MS. CHIN-CAPLAN: Right.

11 THE WITNESS: Right.

12 BY MS. CHIN-CAPLAN:

13 Q Here did they try to recover measles virus
14 from mononuclear sites on day seven and later after
15 the onset of the rash, and they indicate it's
16 difficult to isolate measles virus from plasma or
17 cerebral spinal fluid using these sensitive methods.

18 A After the onset of rash. that's different
19 than after the initiation of infection. The rash
20 lasts about five days. That's what I said, once the
21 onset of the rash then you rapidly are much less
22 likely to recover the virus because you've got the
23 immune response that's clearing the virus.

24 Q If you know this, that it's difficult to
25 obtain it after seven days, wouldn't it be more likely

2843A

GRIFFIN - CROSS

1 that when Afzal and D'Souza did their work that there
2 was not going to be a high likelihood of recovery?

3 A It depends on if your hypothesis which it
4 seems to be is that there is persistent measles virus
5 replication and persistent measles virus, then you
6 ought to be able to recover it whenever. In other
7 persistent virus infections you can always recover the
8 virus.

9 So if the hypothesis is that this is
10 persistent measles virus infection, it doesn't matter
11 when. During acute measles virus you get clearance of
12 the virus and then you can no longer recover it.

13 Q Okay. But even here, it says that it's
14 difficult after the onset of the rash to isolate
15 measles virus from plasma or cerebrospinal fluid.

16 A Right.

17 Q The onset of the rash is the onset of the
18 immune response. You rapidly lose your ability to
19 recover, this is infectious virus, to recover
20 infectious virus after that period of time. Those are
21 facts.

22 Q Okay.

23 Doctor, you indicated that you were writing
24 a chapter or book with Dr. Oldstone?

25 A Yes we're just editing a book.

GRIFFIN - CROSS

1 Q And Dr. Oldstone is a very well known
2 virologist, isn't he?

3 A Yes.

4 Q He's published a great deal on viral
5 persistence, hasn't he?

6 A Uh huh.

7 Q And Doctor, this has been read before, and
8 I'm going to show you Petitioner's Exhibit 61, Tab VV.

9 (Pause.)

10 Doctor, if you just read along with me here.

11 A Where are you reading?

12 Q In the introduction. Let's start with the
13 second full paragraph. It says that the three
14 foundations upon which the understanding of persistent
15 infection rests are first the host immune response
16 fails to form or fails to purge virus from the
17 infected host. Thus viral persistence is synonymous
18 with invasion of the host immunologic surveillance
19 system.

20 Would you agree with that?

21 A That's one mechanism. We talked about that
22 for the immunosuppressed children who are exposed to
23 measles or a measles vaccine can develop, if you don't
24 induce an immune response, if you're unable to induce
25 an immune response, that is certainly one mechanism

GRIFFIN - CROSS

1 for persistence.

2 Q So you don't disagree with it.

3 A No.

4 Q And then it says recent advances have shed
5 light on the cellular molecular players involved.
6 Second, viruses can acquire unique components or
7 strategies of replication. That is viruses can
8 regulate expression of both their own genes and host
9 genes to achieve residence in a nonlytic state within
10 the cells they infect.

11 You would agree with that, right?

12 A Right. He's mainly talking about
13 lymphocytic choriomeningitis virus there which is what
14 he studies.

15 Q Right.

16 Third, the type of diseases that persistent
17 viruses cause are often novel and unexpected. Would
18 you agree with that?

19 A They can be, sure. You have to know that
20 the virus is there in the organ that's relevant.

21 Q Okay. And Doctor, if you go further down,
22 the next sentence, the continuous replication of a
23 viral foreign gene in a differentiate cell can
24 selectively disorder the functions of that cell
25 without destroying it.

2846A

GRIFFIN - CROSS

1 A He's shown that with LCMV.

2 Q Okay.

3 Several examples of viruses that interfere
4 with the ability of neurons to make neuro
5 transmitters.

6 A That's what he did with LCMV.

7 Q Okay.

8 A But there was no problem with showing the
9 virus was there.

10 Q The result is a disturbance in the host
11 biologic equilibrium. Thus one important direct
12 affect of persistent virus replication is to disorder
13 the normal homeostasis of the host and thereby cause
14 disease without destroying the infected cell. Would
15 you agree with that?

16 A As I say, these are all very virus specific
17 types of things, but you can find examples.

18 Q The next sentence down, associated disorders
19 and synthesis or release of cytokines, antibodies and
20 other molecules made by immune cells can lead to
21 either immunosuppression on the one hand, or
22 hyperimmune, autoimmune responses on the other. That's
23 --

24 A In isolated incidences.

25 Q You don't disagree with any of that.

GRIFFIN - CROSS

1 A No.

2 Q Okay.

3 MS. CHIN-CAPLAN: If I can have a minute,
4 Your Honor.

5 SPECIAL MASTER HASTINGS: All right. For
6 any of you at home who may be signing off before we
7 end here, I'll let you know we will be starting again
8 tomorrow morning at 9:00 a.m..

9 MS. CHIN-CAPLAN: Special Master, can I just
10 have a five-minute break so I can find this document?
11 It's somewhere in my papers.

12 SPECIAL MASTER HASTINGS: All right. Let's
13 take a five-minute break.

14 (Whereupon, a short recess was taken.)

15 SPECIAL MASTER HASTINGS: All right. We
16 finished our short break here, and we're going to
17 continue with the cross-examination of Dr. Griffin by
18 Ms. Chin-Caplan.

19 BY MS. CHIN-CAPLAN:

20 Q Dr. Griffin, can I ask you to just read this
21 editorial?

22 A The whole editorial?

23 Q Yes.

24 SPECIAL MASTER HASTINGS: Wait a minute.
25 Let's mark this first.

GRIFFIN - CROSS

1 THE WITNESS: Come on. It's four pages
2 long.

3 SPECIAL MASTER HASTINGS: Wait a minute
4 here. Just wait, okay? First we're going to mark
5 this, and it's Petitioner's Trial Exhibit what? Where
6 are we at? No, 16 was Dr. Verstraeten's letter, so I
7 think it's Petitioner's Trial Exhibit 17.

8 (The document referred to was
9 marked for identification as
10 Petitioner's Trial Exhibit
11 No. 17 and was received in
12 evidence.)

13 SPECIAL MASTER HASTINGS: And, Ms. Chin-
14 Caplan, as Dr. Griffin just said, this is three pages,
15 very, very long pages, lots on the page. You don't
16 seriously want her to read the whole thing into the
17 record? I mean, we're going to file this, so it's
18 going to be in the record.

19 MS. CHIN-CAPLAN: Okay.

20 SPECIAL MASTER HASTINGS: It's in the record
21 as soon as it's filed.

22 MS. CHIN-CAPLAN: I shall target everything.

23 SPECIAL MASTER HASTINGS: Okay.

24 MS. CHIN-CAPLAN: I'm really looking at the
25 section that begins on page 122. It talks about

GRIFFIN - CROSS

1 constellation features which make up the MINE
2 syndrome.

3 SPECIAL MASTER HASTINGS: All right. I see
4 that. Do you see that on page 122?

5 THE WITNESS: Unfortunately, MINE syndrome
6 isn't something that I've heard of.

7 SPECIAL MASTER HASTINGS: I'm sorry. I
8 didn't hear what you said, Doctor.

9 THE WITNESS: I just said the MINE syndrome
10 is something I've never heard of.

11 SPECIAL MASTER HASTINGS: All right.

12 THE WITNESS: So I'll get educated.

13 (Pause.)

14 THE WITNESS: So can you tell me where this
15 was actually? They're quoting all these virus
16 isolations.

17 BY MS. CHIN-CAPLAN:

18 Q Are you through reading, Doctor?

19 A What?

20 SPECIAL MASTER HASTINGS: What did you --

21 THE WITNESS: I don't know what you're
22 trying to --

23 SPECIAL MASTER HASTINGS: What did you want
24 her to read? The whole?

25 MS. CHIN-CAPLAN: I guess I can stop, and if

GRIFFIN - CROSS

1 you need to read, then you let me know, okay?

2 SPECIAL MASTER HASTINGS: Okay. That sounds
3 like a good idea.

4 MS. CHIN-CAPLAN: Okay.

5 BY MS. CHIN-CAPLAN:

6 Q Now, Doctor, do you recognize Dr. Paul
7 Dyken?

8 A No.

9 Q Do you know that he is a pediatric
10 neurologist?

11 A No.

12 Q Do you know that he maintains the SSPE
13 registry for the United States?

14 A No.

15 Q So, Doctor, in this article, is he comparing
16 SSPE to what he calls measles-induced neuroautistic
17 encephalopathy?

18 A I guess so.

19 Q Okay. And the acronym is MINE, M-I-N-E,
20 correct?

21 A I guess so. As I say, it's something I'm
22 unfamiliar with.

23 Q Okay.

24 A Not mainstream, put it that way.

25 Q Yes. And, Doctor, he's essentially

GRIFFIN - CROSS

1 describing the autistic enterocolitis population,
2 isn't he?

3 A Well, it looks like it. As I say, I haven't
4 had a chance to read it in depth, but glancing at it,
5 it looks like what he's doing.

6 Q Uh-huh. And if you go to page 123, on the
7 first full paragraph, he says, "An opinion can be
8 given that MINE develops in the same fashion as does
9 SSPE. Although the syndromes are different, the
10 etiology and the pathogenesis are similar. For both
11 syndromes, two factors are required: an immature or
12 defective immune system which is unable to inactivate
13 the attacking measles virus, whether it is the wild or
14 the live attenuated form.

15 "In the situation of SSPE, the full
16 antigenic wild virus is only partially inactivated,
17 allowing the remaining aborted form to escape and
18 harbor within the large neurons of the cerebral cortex
19 where they are sheltered and persist to grow."

20 And we know that happens in SSPE, correct?

21 A Correct.

22 Q And then if you go to the next column, nine
23 lines down, he states, "Those who develop MINE do not
24 completely neutralize the live attenuated virus and an
25 aborted form of the virus ensues."

GRIFFIN - CROSS

1 A Okay. What I'm trying to figure out is
2 where the proof is that the virus is in the brain.

3 Q This is what he's saying, isn't that true,
4 reading what his statement is?

5 A No, no, no. But "An opinion can be given."
6 This is his opinion.

7 Q And that's what I'm saying, Doctor. I am
8 reading what he has written, is that true?

9 A Right. But I'm just saying it's his
10 opinion. He doesn't have data.

11 Q Okay.

12 A I'm big on data.

13 Q "The aborted form escapes and harbors in the
14 nervous system in particularly susceptible areas such
15 as the hippocampus, limbic system and older portions
16 of the cerebral cortex where the blood-brain barrier
17 is less protective." Have I read that correctly?

18 A You actually read quite well.

19 Q Thank you. Okay. And then further down,
20 Doctor, approximately a third of the way down, there's
21 a sentence that begins, "Opposed to the lengthy period
22 of quiescence seen in SSPE, when the escape of the
23 aborted, partially damaged wild measles virus acts
24 upon the larger neurons residing in neocortical areas,
25 the interval period in MINE is only a matter of

GRIFFIN - CROSS

1 months.

2 "It would appear that breakout is not as
3 devastating as in SSPE, and the clinical symptoms
4 after the short interval may be more due to chronic
5 sapping of the selected host cell's metabolic
6 activity." I read that correctly?

7 A You did.

8 Q Yes. Now, Doctor, in Michelle Cedillo's
9 case, measles RNA was recovered in her gut, wasn't it?

10 A Measles was reported to have been found by
11 RT-PCR in her gut.

12 Q Yes.

13 A But as I think I emphasized, I think it's a
14 result that is highly suspect.

15 Q Okay.

16 A And it's the only thing that links it to
17 measles.

18 Q Yes.

19 A Her whole case.

20 Q Yes.

21 A Okay. So a lot hangs on it.

22 Q And, Doctor, do you know that Michelle has
23 bowel symptoms?

24 A Yes.

25 Q And do you know that she has recently

GRIFFIN - CROSS

1 started treatment with Humira for inflammatory bowel
2 disease?

3 A Yes. It's sort of amazing that you'll
4 immunosuppress somebody you think has a persistent
5 virus infection.

6 Q But, Doctor, you do know that?

7 A Yes.

8 Q Yes. So, in your opinion, and you can
9 certainly tell me whether you have an opinion or not,
10 do you believe that the positive measles finding in
11 the gut is related to her inflammatory bowel disease?

12 A No. I don't think it's a positive measles
13 finding in the gut. I mean, I don't believe that
14 result, put it that way.

15 Q Okay.

16 A So, therefore, I don't think there's a link.

17 Q Well, Doctor, if I asked you to assume that
18 fact, that is, that real finding, that it's true --

19 A Okay. All right.

20 Q -- would you assume then that her
21 inflammatory bowel symptoms are related to the
22 measles?

23 A No, because on the biopsy, there was no
24 evidence of inflammation of measles virus pathologic
25 changes, I mean, nothing that would suggest that would

GRIFFIN - CROSS

1 give her all these symptoms.

2 Q Well, let me ask you this question, Doctor.

3 If you assume that there is positive measles virus

4 recovered in CSF, blood and gut, would you believe

5 that --

6 A Has there been positive virus recovered?

7 SPECIAL MASTER HASTINGS: Let her ask. It's

8 a hypothetical.

9 THE WITNESS: Okay.

10 BY MS. CHIN-CAPLAN:

11 Q Would you assume that if a child had a

12 neurological condition that it was related to the

13 positive measles virus that was found in the CSF?

14 A Well, I think if you found measles in the

15 CSF of this child, that would be a very significant

16 finding, and you'd want to make sure that was true.

17 You would expect to see a lot of other things related

18 to a persistent virus infection of the nervous system

19 like changes on EEGs, scanning of various varieties

20 and increased production of antibody in the CSF, which

21 you would have done on the same sample I assume.

22 But absolutely, if you're finding it in the

23 nervous system, then that would be an important

24 observation, and it should definitely be followed up

25 and figured out.

2856A

GRIFFIN - CROSS

1 MS. CHIN-CAPLAN: Okay. Thank you. I have
2 no further questions, Special Master.

3 SPECIAL MASTER HASTINGS: All right. Any
4 questions?

5 (No response.)

6 SPECIAL MASTER HASTINGS: Ms. Chin-Caplan,
7 you put up on the board an excerpt from Exhibit R, Tab
8 18.

9 MS. CHIN-CAPLAN: Exhibit R. I'm sorry.

10 SPECIAL MASTER HASTINGS: Tab 18. You asked
11 some questions about transient symptoms. Mr.
12 Shoemaker, you know what I'm talking about?

13 MR. SHOEMAKER: I'll try to get to it, sir.

14 SPECIAL MASTER HASTINGS: Okay.

15 MS. CHIN-CAPLAN: Oh, that's the chapter in
16 Fields Virology by Dr. Griffin.

17 SPECIAL MASTER HASTINGS: Yes. Yes, it was.
18 Okay. Can you put that back up?

19 (Pause.)

20 SPECIAL MASTER HASTINGS: The page number
21 that you had? I never heard a page number.

22 MR. SHOEMAKER: Fourteen twenty-seven.

23 SPECIAL MASTER HASTINGS: Oh, it was 27.

24 MS. CHIN-CAPLAN: Fourteen.

25 SPECIAL MASTER HASTINGS: Yes. Fourteen

2857A

GRIFFIN - CROSS

1 twenty-seven. All right. That's what I heard, but I
2 thought someone said that that was -- but that is the
3 correct page. Can you highlight the part that you had
4 highlighted before just as a lead here for me?

5 All right. So do you have that in front of
6 you, Doctor? It's the lower right-hand corner of the
7 page.

8 THE WITNESS: Uh-huh.

9 SPECIAL MASTER HASTINGS: You were asked
10 about this sentence, beginning of the paragraph,
11 "Administration of standard doses of live attenuated
12 MV vaccine results in transient lymphopenia." You
13 were asked about that.

14 THE WITNESS: Right.

15 SPECIAL MASTER HASTINGS: The second clause
16 there, "Suppression of delayed hypersensitivity skin
17 test responses to recall antigens." Now, in the first
18 one, you said transient lymphopenia.

19 THE WITNESS: Uh-huh.

20 SPECIAL MASTER HASTINGS: Lymphopenia I
21 should say.

22 THE WITNESS: Right.

23 SPECIAL MASTER HASTINGS: In this one, you
24 don't use the word transient, but is this a transient
25 effect?

2858A

GRIFFIN - CROSS

1 THE WITNESS: Yes.

2 SPECIAL MASTER HASTINGS: The next clause,
3 "Decreases in antigen and mitogen-stimulated
4 proliferation of lymphocytes." Is that also
5 transient?

6 THE WITNESS: Yes.

7 SPECIAL MASTER HASTINGS: And then the
8 fourth clause, "Altered cytokine production." Was
9 that also transient?

10 THE WITNESS: Yes. Yes.

11 SPECIAL MASTER HASTINGS: All right. All
12 right. I don't have anything further for this
13 witness. Did you have any redirect?

14 MR. MATANOSKI: I did, sir. However, having
15 been handed this editorial that it seems like it would
16 have been in the case-in-chief, perhaps attached to
17 Dr. Kinsbourne's report since it talks about some
18 postulate of SSPE or measles persistence that's
19 associated with autism, I'd like to actually have
20 Dr. -- I hate to do this.

21 I'd like to have Dr. Griffin take a closer
22 look at it as I just have and before I ask her
23 questions offer any opinions she might have on this
24 after taking a further review. So I hate to do it,
25 sir, but I'd ask for just a few minutes to let her

GRIFFIN - CROSS

1 take a quick look at this.

2 SPECIAL MASTER HASTINGS: Well, I was kind
3 of stunned to see this editorial. This seems to be
4 new evidence offering at least some support to your
5 theory of the case. It's a three-year-old editorial,
6 and it comes in at 7:00 on the last day of trial. It
7 seems surprising to say the least. So, in those
8 circumstances, what kind of a break are you talking
9 about?

10 MR. MATANOSKI: I'd just like about five
11 minutes so that Dr. Griffin can take a look at it.

12 SPECIAL MASTER HASTINGS: All right. Let's
13 take a five-minute break. And if you decide you want
14 to file something, a written report later on to
15 respond to this --

16 THE WITNESS: I was going to say maybe we
17 could do that. I'd be glad to write something.

18 SPECIAL MASTER HASTINGS: Please, Doctor,
19 one of us can only talk at a time or the reporter
20 can't get it down. If you decide you'd rather have a
21 written response to this at a later date, that would
22 be acceptable too.

23 MR. MATANOSKI: Actually, sir, that probably
24 would be the better way to do that so that Dr. Griffin
25 doesn't have to be put on the spot here to read

GRIFFIN - REDIRECT

1 quickly and digest this all at once.

2 And in fact, sir, that may make it
3 unnecessary for the second part of what I was going to
4 talk about with respect to this particular document,
5 which is that this may require rebuttal testimony by
6 other witnesses that I had released at this point
7 based on the notion that there would not be rebuttal
8 by Petitioners' witnesses in those areas since this
9 touches also on areas beyond measles virology it would
10 seem.

11 But if we were to permit us to take a look
12 at this or if you were to permit us to take a look at
13 it, have our experts review it and if necessary reply
14 by written report, I think that would take care of
15 that as well, sir.

16 SPECIAL MASTER HASTINGS: All right. Well,
17 we'll permit such a thing because of the time at when
18 this document is coming in.

19 MR. MATANOSKI: Thank you, sir. Then I only
20 have a few questions.

21 SPECIAL MASTER HASTINGS: Okay. Go ahead.

22 REDIRECT EXAMINATION

23 BY MR. MATANOSKI:

24 Q I think the last article you were looking at
25 in response to the Special Master's questions, he went

2861A

GRIFFIN - REDIRECT

1 through that these were all transient changes. There
2 was also a further sentence in that paragraph that you
3 were looking at in Fields Virology. I believe that
4 sentence went to whether or not you believed these
5 changes were clinically relevant.

6 A I don't have it up in front of me.

7 Q I know. I know you don't.

8 A But I do not think that these changes are
9 clinically relevant.

10 Q I just want you to affirm or not whether you
11 believe those changes are --

12 A I do not think they're clinically relevant.

13 Q With respect to there was some discussion
14 about memory response, do you think they're clinically
15 relevant changes after the induction of measles
16 vaccine in this memory response?

17 A No.

18 Q Is anything in your opinion with regard to
19 the PCR based on access that you've had to materials
20 through the MMR litigation in the United Kingdom?

21 A Not that I know of.

22 Q You didn't use any of that material in
23 writing your report?

24 A I did not.

25 Q You mentioned that Dr. Wakefield asked you

GRIFFIN - REDIRECT

1 to come over to look at his --

2 A Yes. That was very early. I think it was
3 probably 1998. He had a meeting that he used to have
4 at Wellcome Trust, which was funding him early on, and
5 he would invite somebody to be speaker basically or an
6 outside person, and so I was invited one year and I
7 was aware of the controversy. And as I say, it was
8 early on when he was just beginning to implicate MMR
9 as a cause of autism, and so I was curious, so I went.

10 I spoke, I interacted with the people in the
11 lab. They were having a lot of trouble trying to make
12 their PCR work. They couldn't reproduce the
13 immunocytic chemistry that they had one slide of in
14 the gut. I mean, they presented those data at that
15 conference. It was an open scientific meeting. So I
16 had a little bit. I had nothing else to do with it
17 after that, but I had a little bit of insight, a
18 little bit of knowledge about sort of the lab and the
19 thinking and that sort of thing.

20 Q Were they recovering measles virus?

21 A No. No, I mean, if you really want to know,
22 I mean, frankly, they did not have a hypothesis of
23 what the connection -- at that time, they did not have
24 a hypothesis of the connection between MMR and measles
25 and autism and were sort of looking for something that

GRIFFIN - REDIRECT

1 would link them.

2 Q With respect to the Uhlmann study, you were
3 asked some questions and you looked through your
4 report. I understand you to say that sequencing was a
5 problem from what you could see in publicly available
6 information and other factors, only publicly available
7 information. Did you see other --

8 A Right. Well, the blinding of the samples is
9 really a critical thing because if people know which
10 ones are the patients and which ones are the controls,
11 and there was no evidence in that paper that those
12 samples were blinded or coded or something, I mean,
13 all of us have to do that because we're prejudiced.
14 We're looking for something. We have a hypothesis.
15 We would like for it to be proved. So it's just a
16 very critical part of data collection.

17 Q You were presented with a series of
18 statements from Dr. Oldstone in something that he had
19 published I think recently. Now you're working with
20 Dr. Oldstone in publishing some work on virology, is
21 that right?

22 A Right. Well, yes. We're colleagues. I
23 mean, we're in the same field basically. I've known
24 him for a long time.

25 Q Okay. That series of statements that you

GRIFFIN - REDIRECT

1 were asked if you agreed whether or not they were
2 written there, could you comment on that series of
3 statements with respect to measles virus?

4 A Well, those are all very generalized
5 statements about the whole world of virology, so I
6 don't know how many different hundreds of viruses can
7 cause of infections of all different varieties. And
8 you can certainly find examples of them that would do
9 each of these things. He has mainly studied a mouse
10 virus, which is lymphocytic choriomeningitis virus
11 where he infects the animals at a very early age and
12 then he can see developmental abnormalities with that
13 particular mouse virus.

14 And so I don't disagree with that, but none
15 of them have been observed. I mean, it's not very
16 relevant or very specific. It certainly isn't
17 specific for measles, and so these are very general
18 statements that are true for one virus or another, but
19 you can't conclude that all of them could be true for
20 measles.

21 Q As far as wild measles virus is concerned,
22 is there any reason to conclude that gastrointestinal
23 symptoms that are observed were caused by the wild
24 measles virus?

25 A The gastrointestinal?

GRIFFIN - REDIRECT

1 Q Were caused by the virus itself, the wild
2 measles virus itself?

3 A Right. There hasn't been evidence of that
4 because diarrhea itself is not usually a component of
5 measles without the secondary infection.

6 Q How about the same question, but this time
7 it's a vaccine virus?

8 A Oh, I don't know that there's any evidence
9 that diarrhea is -- I mean, the wild type virus,
10 diarrhea is associated with the disease, but that's
11 not true with vaccination.

12 Q How long have you studied measles virus?

13 A Probably about 30 years.

14 Q Okay. In your study of measles virus over
15 that period of time, I understand you've studied it in
16 population, right, and in the lab. You've also
17 studied vaccine virus. Any reason in your mind after
18 30 years of study to conclude that persistent measles
19 virus would result in autism?

20 A No.

21 MR. MATANOSKI: Thank you. I have no
22 further questions.

23 SPECIAL MASTER HASTINGS: Anything further
24 for this witness, Ms. Chin-Caplan?

25 MS. CHIN-CAPLAN: Two questions.

GRIFFIN - RECROSS

1 SPECIAL MASTER HASTINGS: Okay.

2 RECROSS EXAMINATION

3 BY MS. CHIN-CAPLAN:

4 Q Doctor, you indicated that there was a
5 problem with blinding in the Uhlmann study. Where is
6 that located in his article?

7 A Well, what you look for is that they say
8 they did it. I mean, anybody that does it makes sure
9 people know that.

10 Q Wouldn't you assume that they would act in
11 accordance with the standards of their profession?

12 A All I have to say is there are a lot of
13 publications out there from people who don't blind
14 samples, and it's a problem. And so I can't assume
15 that. I cannot assume that. All I can say is if
16 people blind samples, they make sure that it's stated
17 in the methods.

18 Q Do you know the reputation of the O'Leary
19 lab at all?

20 A Oh, yes.

21 Q And what is the reputation?

22 A It's not very good.

23 Q That's what you're saying? It's not very
24 good?

25 A Right. The reputation. You're asking about

GRIFFIN - FURTHER REDIRECT

1 the general reputation in the scientific community?

2 Q Yes.

3 A Absolutely. Yes.

4 Q And, Doctor, you indicated that you went to
5 see Dr. Wakefield in was it 1998?

6 A Well, no, I wouldn't want to be held to the
7 date, but it was very early in this, putting forward
8 this hypothesis that MMR caused -- and at that time,
9 it was specifically MMR, the measles component of MMR,
10 which I guess is the persistent hypothesis.

11 Q And at that time, Doctor, were you a member
12 of the Scientific Affairs Committee for Merck?

13 A I was a member of their Scientific Advisory
14 Board at Merck for a period of three or four years,
15 and I have no idea whether that overlapped or not.
16 I'd have to go back to my calendar to figure that out.

17 Q Okay. And Merck makes the MMR, doesn't it?

18 A In the U.S., but in the U.K., there's three
19 vaccine manufacturers.

20 MS. CHIN-CAPLAN: Okay. Thank you.

21 SPECIAL MASTER HASTINGS: Anything further
22 for this witness?

23 MR. MATANOSKI: Just one followup.

24 FURTHER REDIRECT EXAMINATION

25 BY MR. MATANOSKI:

GRIFFIN - FURTHER REDIRECT

1 Q With respect to that last question, was your
2 opinion of the work done by Dr. Wakefield influenced
3 in any way by being on the Science Advisory Board or
4 being somehow Science Advisory personnel for Merck?

5 A No. No, not at all. That's irrelevant.

6 MR. MATANOSKI: That's it, sir.

7 (Witness excused.)

8 SPECIAL MASTER HASTINGS: All right. I
9 think we're done for the day. Let me ask Ms. Chin-
10 Caplan, now tomorrow morning you're planning to
11 present some more testimony from Mrs. Cedillo, is that
12 correct?

13 MS. CHIN-CAPLAN: That's correct, Special
14 Master.

15 SPECIAL MASTER HASTINGS: Anything else?

16 MS. CHIN-CAPLAN: Aside from closing, no,
17 that's it.

18 SPECIAL MASTER HASTINGS: And then the
19 closing argument. All right. So we're done for the
20 day here. We'll start again at 9:00 a.m. tomorrow.
21 We're adjourned.

22 MR. MATANOSKI: Thank you.

23 (Whereupon, at 7:15 p.m., the hearing in the
24 above-entitled matter was adjourned, to reconvene on
25 Tuesday, June 26, 2007, at 9:00 a.m.)

REPORTER'S CERTIFICATE

DOCKET NO.: 98-916V
CASE TITLE: Theresa Cedillo v. HHS
HEARING DATE: June 25, 2007
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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