

UNITED STATES COURT OF FEDERAL CLAIMS

THERESA CEDILLO AND MICHAEL)
CEDILLO, AS PARENTS AND)
NATURAL GUARDIANS OF)
MICHELLE CEDILLO,)

Petitioners,)

v.)

Docket No.: 98-916V

SECRETARY OF HEALTH AND)
HUMAN SERVICES,)

Respondent.)

Pages: 1214 through 1557

Place: Washington, D.C.

Date: June 18, 2007

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IN THE UNITED STATES COURT OF FEDERAL CLAIMS

THERESA CEDILLO AND MICHAEL)
 CEDILLO, AS PARENTS AND)
 NATURAL GUARDIANS OF)
 MICHELLE CEDILLO,)
)
 Petitioners,)
)
 v.)
)
 SECRETARY OF HEALTH AND)
 HUMAN SERVICES,)
)
 Respondent.)

Docket No.: 98-916V

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

Monday,
 June 18, 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

APPEARANCES:

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C O N T E N T S

| <u>WITNESSES:</u> | <u>DIRECT</u> | <u>CROSS</u> | <u>REDIRECT</u> | <u>RECROSS</u> | <u>VOIR DIRE</u> |
|----------------------------|---------------|--------------|-----------------|----------------|------------------|
| <u>For the Respondent:</u> | | | | | |
| Eric Fombonne | 1239 | 1365 | 1448 | -- | -- |
| Edwin Cook | 1466 | 1509 | 1554 | -- | -- |

E X H I B I T S

| <u>RESPONDENT'S EXHIBITS:</u> | <u>ADMITTED</u> | <u>RECEIVED</u> | <u>DESCRIPTION</u> |
|-----------------------------------|-----------------|-----------------|--------------------|
| 8 | 1238 | -- | Slide |
| 9 | 1459 | 1459 | Slide |
| 10 | 1489 | 1489 | Slide |

1 for the Respondent Dr. Fombonne and Dr. Cook today.
2 Tomorrow will be a single witness, Dr. Wiznitzer.
3 Wednesday will be Dr. Bustin and Dr. Ward. Thursday
4 we will have Dr. Hanauer and possibly Dr. McCusker.
5 On Friday, we will have Dr. Brent, and if Dr. McCusker
6 doesn't testify Thursday, he'll testify Friday.

7 It's possible that Dr. Chadwick will testify
8 Friday. He may or may not testify. The Petitioners
9 have withdrawn their request to cross-examine Dr.
10 Chadwick. Then on Monday, we will have Dr. Griffin
11 and Dr. Fombonne again for the Respondent. So that's
12 the changes in the schedule.

13 With that, we're going to go into the
14 government's case. Mr. Matanoski, you had reserved
15 the right to make a second part of your opening at the
16 beginning of your case. Do you want to do that?

17 MR. MATANOSKI: Yes, sir, I do.

18 SPECIAL MASTER HASTINGS: Okay. Why don't
19 you go ahead and do so at this time.

20 MR. MATANOSKI: Thank you, sir. Good
21 morning. Over the weekend, we thought about our case.
22 We seriously considered at this point making a motion
23 for judgment on the record as it stands. We believe
24 that under the precis of Daubert, you have not heard
25 evidence which you can rely on to reach a decision in

1 the Petitioners' favor.

2 At every critical juncture, their evidence
3 has failed in that test. At every critical juncture,
4 their evidence has not been scientifically reliable.
5 Nevertheless, we decided that we should go on and
6 present the case, albeit a little more tailored, a
7 little more limited than the case we had anticipated.

8 We're putting on a case anyway for several
9 reasons. The first is I'll call it bait and switch,
10 because long ago when this Court was convening the
11 Omnibus Autism Proceeding, you were told by the PSC
12 that there would be a general causation proceeding,
13 that it would encompass all their theories of
14 causation. You would have before you evidence that
15 you could use in each and every case pending before
16 you.

17 Late in the proceeding, there was a change.
18 The PSC decided that they would go with a test case,
19 which the Respondent had advocated from the beginning,
20 a test case approach, an approach that we could have
21 begun many years ago.

22 They did tell you this, though, that their
23 test case would be applicable to a number of other
24 cases, a significant number, that this test case that
25 you would hear could be applicable to 80 percent of

1 one firm's cases, yet throughout the direct
2 examination of their witnesses, there was a concerted
3 effort to limit the testimony to one specific case.
4 They were resistant to expanding their testimony and
5 their evidence beyond this case. Again, bait and
6 switch.

7 This is going to be applicable to a
8 significant number of cases, but the testimony that
9 was coming in was applicable only to this case. It's
10 only through dogged cross-examination that we were
11 able to expand the evidence before you so that it
12 could be used in other cases.

13 We intend to give you evidence that you can
14 use in other cases. We intend to give you good
15 scientific evidence this morning and throughout this
16 coming week and into next week that you can use in a
17 large number, if not all, of the upcoming cases. In
18 the end, this case will profoundly and significantly
19 affect the other cases pending before you because of
20 that evidence.

21 There's another reason. We were told,
22 similar to the reason I just went through, that this
23 case was going to have broad application. We don't
24 want you to make a decision on a case having such
25 broad application on bad science, on the lack of

1 reliable evidence. We don't want that decision to
2 come out because you say, you know, I don't have good
3 science upon which to make up my mind, so therefore, I
4 can't find for Petitioners.

5 We want you to make that decision on good
6 evidence, on good, reliable scientific evidence. We
7 want you to be sure in your own mind that MMR vaccine
8 is not causing autism because you've had good evidence
9 to look at and consider on that.

10 What is good evidence? What is good
11 scientific evidence? It's evidence based on research.
12 It's evidence based on research that's been reduced
13 to writing, exposed to the scientific community,
14 tested, scrutinized, reviewed, discussed, reproduced.

15 It's evidence from those who have experience
16 in the area that they're testifying in, those who
17 treat autistic children, those who research autism to
18 try to find its cause and its cure, from those who
19 work in immunology on a daily basis, from those who
20 treat children with immunological disorders, from
21 those who work directly with PCR, who know how it
22 works, when it's reliable and when it isn't, not from
23 those who testify for a living.

24 Now it's true that some of the experts
25 you're going to hear from us have testified. By the

1 fact that they're coming in here, it would be an
2 impossibility for you to hear an expert who hasn't
3 testified at some point because they're in the Court
4 testifying before you. The important point is they
5 don't do it for a living. They do it within their
6 subject matter. They do it when it's important and
7 that's it.

8 A third reason why we're going to go ahead
9 with our evidence is a public policy reason. A
10 serious accusation has been leveled. A serious
11 accusation has been leveled against an important part
12 of the public health arsenal against a preventable
13 disease. An accusation has been leveled that MMR
14 vaccine causes autism. That accusation must be
15 answered, and we will answer it.

16 It's serious and it's important, the issue
17 before you. You know that. It's certainly important
18 to the Cedillos. It's important, though, for another
19 reason. This accusation goes against a vaccine that
20 is designed to prevent a killing disease.

21 We forget that in this country because we've
22 been very fortunate. We have not suffered a measles
23 outbreak of any great measure in many, many years.
24 The world does not enjoy our fortune. Four hundred
25 and fifty thousand people die every year from measles,

1 450,000. Almost a half a million people die every
2 year from a preventable disease.

3 The threat remains real in this country. It
4 remains real, and we can tell that from the experience
5 that Great Britain had. The United Kingdom went
6 through a scare about measles-mumps-rubella vaccine.
7 That scare was based on bad science. That scare was
8 based on the work primarily of one man, Andrew
9 Wakefield.

10 What happened in Great Britain can happen
11 here. What happened there was there was a lack of
12 confidence in the MMR vaccine. Vaccination rates
13 dropped. Measles came back, and unfortunately,
14 tragically, several people died.

15 It was bad science that was at the heart of
16 that scare. It was the work, as I said, of Andrew
17 Wakefield. He published an article in 1998 called
18 "Ileal-Lymphoid-Nodular Hyperplasia, Nonspecific
19 Colitis and Pervasive Development Disorder in
20 Children."

21 It doesn't sound that startling from the
22 title, but he knew what the impact was, and the impact
23 was felt immediately. This article, this study that
24 he came forward with, launched a scare, a scare
25 against vaccinating children with MMR vaccine. He

1 claimed to find a link between ILNH, ileal-lymphoid-
2 nodular hyperplasia, and autism, and that is what
3 you're hearing in this case, ILNH and autism.

4 Now try as they might, the Petitioners are
5 trying to say that this is not about Dr. Wakefield's
6 study, but his study is at the fore. It catapulted
7 this issue into the public forum. It catapulted this
8 issue into the public's mind.

9 You've heard a bit about what happened with
10 Andrew Wakefield and his report, but I'm going to go
11 back and pull those strands together that you've heard
12 through cross-examination and put it together for you
13 right now in a timeline. I'm going to put it together
14 so you can see how it unfolded, and you are going to
15 see a history that ran from the United Kingdom over to
16 this country where it rests in this courtroom today.

17 In 1996, Andrew Wakefield was approached by
18 attorneys. These attorneys represented several
19 parents who believed that their children's autism was
20 caused by MMR. Why Andrew Wakefield? Why him amongst
21 other physicians? Because he had previously tried to
22 show that measles vaccine caused Crohn's disease. He
23 was unsuccessful in that, but the attorneys knew they
24 had their man.

25 They went to him. They offered him money to

1 look at their cases and consult with them. He went on
2 to file a patent. In 1997, he filed a patent for a
3 monovalent measles vaccine, a vaccine that would
4 directly compete with the MMR vaccine, a vaccine he
5 would stand to substantially be enriched if the MMR
6 vaccine were to fall into disuse.

7 In 1998, he published his study, "ILNH
8 Nonspecific Colitis and Pervasive Developmental
9 Disorders in Children." He published it in a very
10 influential journal, the *Lancet*. I'm sure in your
11 work in vaccine cases you've heard of that journal
12 before.

13 He did not reveal at that time that he had
14 been contacted and received money from lawyers, a
15 material omission in the view of the editors when they
16 found that out later on. He did not of course reveal
17 that he had a patent for a competing vaccine to MMR.
18 He went ahead and presented this without revealing
19 those critical facts.

20 They relied on it and published their study.
21 He also didn't reveal that several of the children --
22 it was a very small group; there were only 12
23 children -- were actually litigants that were being
24 represented by the attorneys who had given him money.

25 In 2000, he published another article

1 purporting to show the link between MMR and autism.
2 In 2002, his name again appeared on an article that
3 you've seen referenced throughout the reports here,
4 throughout the reports of the experts. It was the
5 Uhlmann article, the PCR article.

6 In 2004, it began to crash down upon him.
7 In 2004, a series of newspaper articles were
8 published, the first one revealing his contact or the
9 fact that he had received money from attorneys who
10 represented litigants bringing cases alleging MMR
11 caused autism.

12 The dogged work of one journalist brought
13 this to the fore. For six years, it had remained
14 hidden. When it was out in public scrutiny, what
15 happened? The co-authors on his original study
16 repudiated the results of that study. They published
17 it in the *Lancet* that they no longer supported the
18 interpretation that it was possible that MMR could
19 cause autism.

20 Dr. O'Leary, whose Unigenetics Lab was
21 publishing these results of finding measles virus in
22 gut biopsies, publicly said he did not support the
23 assertion that MMR vaccine caused autism. They all
24 began to flee from Andrew Wakefield. He alone was
25 left with purporting that there was some connection.

1 It's now in our courtroom. It's made its
2 way across the Atlantic into our courtroom, and we
3 have to deal with it now. But we are going to put on
4 the evidence this morning and throughout this week
5 that will allow you to effectively deal with that and
6 to show you that MMR vaccine is indeed safe. Those
7 are the reasons we're going forward.

8 I want to briefly review some of the
9 evidence you've heard and some of the evidence you're
10 about to hear so that you can see and contrast the
11 reasons why we're going forward and what evidence you
12 will hear that responds to what you heard last week.

13 Dr. Aposhian spent a great deal of time
14 telling us that there were differences between the
15 various species of mercury, yet he conflates them all
16 at the end to reach his conclusions. He takes bits
17 and pieces from various studies about all different
18 kinds of mercury and then comes up with the
19 conclusion.

20 Dr. Brent will address that. Dr. Brent will
21 address systematically why those studies do not equate
22 to the conclusion that thimerosal is causing some sort
23 of immunological dysregulation or dysfunction in
24 children.

25 You heard from Dr. Krigsman. It was

1 somewhat striking or telling when he explained why he
2 came to the conclusion in his thinking that there was
3 a connection between autism and MMR. He said it was
4 in fact the 1998 article from Dr. Wakefield, and he
5 said there was one name on that article that was
6 important to him, and that was the name Walker-Smith.
7 I believe if you look back through the transcript
8 you'll see that.

9 If you check and look at the 2004
10 retraction/repudiation of the 1998 article, you will
11 see that one of the individuals who repudiated that
12 1998 article was Dr. Walker-Smith.

13 Now Dr. Krigsman lacks experience in this
14 area. He does not have extensive experience in
15 reviewing and knowing what actually is inflammatory
16 bowel disease. He boasts one publication, and that
17 publication is not on inflammation in the bowel.

18 You will hear from Dr. Hanauer, who boasts
19 numerous publications in the area of inflammatory
20 bowel disease. He knows what to look for and when
21 there is evidence of it and when there isn't. He will
22 tell you that ILNH is not an uncommon finding. Ileal-
23 lymphoid-nodular hyperplasia is seen quite often. It
24 is not inflammation.

25 You heard from Dr. Hepner, and frankly, I

1 think the PSC may have cringed at one part of her
2 testimony, that is, when she said that MMR vaccine
3 causing autism is an unproven hypothesis. You heard
4 it from their own expert. Our experts are going to go
5 one further than that. They're going to go one step
6 better. They're going to tell you that the theory
7 advanced by the PSC is not biologically possible.

8 Dr. Kennedy. Dr. Kennedy is important for
9 two reasons. One is a procedural one. You've heard
10 some discussion about whether evidence about
11 Unigenetics should come in because some of it was
12 discovered at a late date. Dr. Kennedy knew about
13 Unigenetics back in 2001 or 2002.

14 He testified that he had a full explanation
15 from those in the lab about what they were doing. He
16 certainly had available to him information about how
17 Unigenetics was operating long before we did, the
18 Respondent. You also heard from him about measles
19 virus. He kind of glibly added at the end of his
20 testimony Dr. Griffin has written a hundred articles
21 on this. She's the expert in the area.

22 Well, you're going to hear from Dr. Griffin.
23 She's going to tell you that measles virus can indeed
24 persist in the brain, but when it does, it has a
25 specific clinical presentation, and that presentation

1 is inconsistent with autism. It does not look at all
2 like autism. She'll also tell you that unless
3 treated, the condition is invariably fatal. Measles
4 vaccine doesn't cause autism. When it's in the brain,
5 it kills you.

6 You heard from Dr. Byers. Now she's no
7 stranger to Vaccine Act proceedings. She's been here
8 a number of times. She's always full of surprises,
9 and she didn't fail to disappoint us here last
10 Thursday. She was testifying outside her area of
11 expertise, frankly, but you will hear in contrast
12 people who will testify in their area of expertise to
13 counter what she had to say.

14 You'll hear from Dr. Brent, who is certified
15 in medical toxicology, to address where she went with
16 toxicological issues. You will hear from Dr.
17 McCusker, who is a pediatric immunologist, who will
18 address her immunological testimony. Now, in
19 contrast, Dr. McCusker spends her time working with
20 patients and researching immunology. She does not
21 spend her time in courtrooms testifying about it.

22 Dr. Kinsbourne was supposed to tie it all
23 together. He was the linchpin. He needed to bring
24 all those strands of their case together at the very
25 end. His testimony was very telling.

1 First, he doesn't work much with autism
2 despite him saying he has extensive experience. Check
3 his CV. See how many times he's published on autism.
4 It's about three or four. See how many of those
5 represent original research. It's zero. He's
6 reviewing the work of others.

7 Well, you're going to hear those others, the
8 ones who are actually doing the work in the area.
9 You're going to hear from Dr. Fombonne, who's
10 published countless articles on autism, who treats
11 children with autism, whose life is devoted to
12 researching it.

13 You're going to hear from Dr. Kennedy, who
14 is one of the preeminent, if not the preeminent,
15 experts in autism genetics. You're going to hear from
16 Dr. Wiznitzer, who spends his days treating children
17 who are afflicted with this condition. In the end,
18 you'll have the good science you can rely on to make
19 your determination about whether this theory that's
20 been advanced is accurate or not.

21 SPECIAL MASTER HASTINGS: Mr. Matanoski,
22 while you're pausing here, in between Dr. Fombonne and
23 Dr. Wiznitzer, you mentioned Dr. Kennedy.

24 MR. MATANOSKI: Did I say Kennedy? I meant
25 Cook.

1 SPECIAL MASTER HASTINGS: You meant Dr.
2 Cook.

3 MR. MATANOSKI: I apologize. I certainly
4 apologize to Dr. Cook. Sorry, sir. It's Dr. Cook.
5 Although I know he's pretty modest, he is the one who
6 is preeminent in the field of autism genetics. Thank
7 you, sir.

8 You will also be hearing testimony about
9 Unigenetics because a lot of this case seems to come
10 back to one thing, and that's a positive finding of
11 measles virus genomic material in a gut biopsy sample,
12 and a lot of these strands throughout Petitioners'
13 case have led to this result. That is critical to
14 their case.

15 Dr. Kinsbourne said without that, I would
16 not reach an opinion here that there's causation, and
17 this has to be one of the strongest cases that they
18 could possibly present under this theory. So
19 Unigenetics becomes critical.

20 You will hear from Dr. Bustin. You will
21 hear from Dr. Ward and indeed to some extent from Dr.
22 Chadwick collaterally, if you will, about what
23 reliance you can place on that PCR result that came
24 from Unigenetics.

25 You already know something about the lab.

1 Dr. Kennedy, and this time I did get it right. I do
2 mean Dr. Kennedy. Dr. Kennedy told you it was an
3 entrepreneurial enterprise. It was to make money. It
4 was a sideline by Mr. O'Leary's lab.

5 The problem with Unigenetics is they didn't
6 do what they were supposed to do. They didn't do it
7 well. I won't go into because it is very complicated,
8 all the different factors about PCR testing, but one
9 take-home that strikes even a layperson as critical is
10 that negative samples, samples known to contain no
11 measles virus, were coming back positive. You heard
12 from Dr. Hepner and Dr. Kennedy that that meant the
13 results are not reliable.

14 There's another thing that bears mentioning
15 right now. You've heard throughout the direct
16 testimony the term plausible. You've heard that
17 mentioned a number of times, and I'm not sure that
18 it's been defined for you. What is meant by
19 plausible?

20 There's a notion that's been developed that
21 plausible and biologic plausibility means possible,
22 that it's biologically possible. In a JZ chain, link
23 after link of mere possibility is created. So at the
24 end, those who are willing to take the witness stand
25 for the Petitioners say I'm right at the cusp of 50

1 percent, but I'm just over it in saying that there's
2 causation after a link of one "well, it's close, but
3 I'm going to say that that makes the 50 percent cut"
4 after another as if this plausibility is really
5 something lower than likelihood, as if it's just
6 something that's biologically possible.

7 Last night, in preparing to address you
8 today, I did something I should have done many years
9 ago when the Federal Circuit and other Courts were
10 using the term plausible, when they were using the
11 term plausible to discuss what it is that you needed
12 to see before you could find causation. What kind of
13 theory? They said a biologically plausible theory.
14 Does that mean a biologically possible theory?

15 I went to the dictionary, which is again
16 where I should have gone years ago, and looked up the
17 definition of plausible. Well, there are two.
18 There's a first definition and a second definition,
19 and I think common understanding is the first
20 definition is the primary one.

21 Well, the primary definition of plausible,
22 and this is from *Webster's New Riverside University*
23 *Dictionary*, is seemingly or apparently valid, likely
24 or acceptable. Think about what you heard. Is it
25 likely? Is it scientifically acceptable?

1 The second definition perhaps is what the
2 Petitioners' experts were after. I don't mean to be
3 glib, but: 2) Giving a deceptive impression of truth,
4 acceptability or reliability, specious. That's what
5 you have right now. Specious. A specious theory.

6 Getting back to where we started, which is
7 good science, and there's not only good reason from
8 the standpoint of reaching a reliable result to using
9 good science. It's legally required. Daubert
10 requires you to use reliable, good science.

11 You haven't heard that so far. You're about
12 to hear that. You're going to hear from experts who
13 spend their time studying autism. You're going to
14 hear from experts who spend their time studying
15 inflammatory bowel disease. You're going to hear from
16 an expert who spends her time working on immunology.
17 Her place of work is a hospital. It's not a
18 courtroom.

19 You're going to hear from experts who know
20 PCR and they know when the results are reliable and
21 when they aren't. In the end, you're going to have
22 good science, you're going to have good evidence, and
23 you're going to find that MMR vaccine is safe. Thank
24 you.

25 SPECIAL MASTER HASTINGS: Thank you, Mr.

1 Matanoski. I assume that Dr. Fombonne will be your
2 first witness then?

3 MR. MATANOSKI: Yes, sir. We'd like to call
4 him now.

5 SPECIAL MASTER HASTINGS: Dr. Fombonne, if
6 you could take the witness stand, please?

7 Before we start the examination, I want to
8 remind all the counsel and any witnesses who are
9 present that in addition to those in the courtroom, we
10 have a number of people listening in by telephone
11 conference call, quite a large number, and we're also
12 recording the audio so people can download that and
13 listen to it over the internet. We appreciate
14 everyone speaking up well, keeping the microphones
15 close to them and speaking up so that those at home
16 listening in can hear as well.

17 With that, let me swear the witness. Dr.
18 Fombonne, would you raise your right hand for me?

19 Whereupon,

20 ERIC FOMBONNE

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

23 SPECIAL MASTER HASTINGS: Okay.

24 MS. RICCIARDELLA: Before we begin, may I
25 approach and give you the handouts that Dr. Fombonne

1 is going to be discussing?

2 SPECIAL MASTER HASTINGS: All right. Thank
3 you. So for the record, we have a handout which goes
4 with Dr. Fombonne's testimony.

5 MS. RICCIARDELLA: He'll be discussing them.
6 There will be slides in addition.

7 SPECIAL MASTER HASTINGS: There will be
8 slides that correspond with this?

9 MS. RICCIARDELLA: Correct.

10 SPECIAL MASTER HASTINGS: Let's mark this.
11 I believe we would be at Respondent's Trial Exhibit 8.
12 (The document referred to was
13 marked for identification as
14 Respondent's Trial Exhibit
15 No. 8.)

16 SPECIAL MASTER HASTINGS: That's my count.
17 Anyone can correct me if I'm wrong on that. We'll
18 refer to that by that exhibit number.

19 MS. RICCIARDELLA: Before we begin, Dr.
20 Fombonne has a soft voice. I just want to make sure,
21 is your microphone on?

22 THE WITNESS: Yes. Can you hear me?

23 SPECIAL MASTER HASTINGS: Can we pin Dr.
24 Fombonne with the --

25 MS. RICCIARDELLA: That's why I was just

1 looking. I think he has it.

2 SPECIAL MASTER HASTINGS: Okay. Very good.

3 MS. RICCIARDELLA: I notice there's one
4 here. Do I need to be wearing this as well?

5 SPECIAL MASTER HASTINGS: I think you're
6 okay.

7 MS. RICCIARDELLA: Okay.

8 DIRECT EXAMINATION

9 BY MS. RICCIARDELLA:

10 Q Good morning, Dr. Fombonne. Would you
11 please introduce yourself to the Court?

12 A My name is Eric Fombonne.

13 Q And would you please state your current
14 academic appointment?

15 A I am a Professor of Psychiatry at McGill
16 University, Montreal, Canada.

17 Q And, Doctor, why are you testifying here
18 today?

19 A I'm testifying because I've been asked by
20 the HHS to provide my evidence based on my research
21 about this allegation of a link between MMR and
22 vaccines in general and autism. I have been involved
23 in that research since I was in the U.K. where I saw
24 the first hypothesis of Wakefield being launched in
25 1998. I was there and was involved in a peer review

1 of his hypothesis at the time.

2 Over the years, I think I've seen two
3 things. My patients have been constantly concerned as
4 parents about the possible role of vaccines as an
5 etiologic factor in the autism in their child, and
6 that is a critical aspect as we have to advise in our
7 clinical practice constantly. In spite of the
8 evidence, we still have to convince parents that it's
9 not associated with it.

10 The second aspect I suppose is the aspect of
11 the impact of public health concerns, which have been
12 quite significant. When I was in the U.K. before I
13 moved to Canada, I saw epidemics of measles in
14 Ireland, for instance. The MMR coverage dropped to
15 very low levels and three young children died in 2000.

16 Again recently, I must say that to
17 complement the information which was given earlier
18 this morning, 18 months ago in the U.S., there was a
19 measles outbreak in one of the midwest states and a
20 number of people became very ill.

21 When the researchers looked at these young
22 children who developed measles in a very significant
23 way, 95 percent of them had not been vaccinated, and
24 when their parents were asked why you did not
25 vaccinate your children, the reason which came, the

1 first one, was the fear of autism. So I think it's a
2 deemed fact. It's still significant abroad, in the
3 U.K. quite certainly, but also here.

4 Q Doctor, you received a Baccalaureate in
5 Science with distinction from the Academy of Paris, is
6 that correct?

7 A Yes. In 1971, yes.

8 SPECIAL MASTER HASTINGS: Dr. Fombonne, can
9 we ask you to do the best you can to speak up a little
10 louder so the folks can hear you?

11 THE WITNESS: Yes. I know. I know.

12 MS. RICCIARDELLA: He has a soft voice.

13 SPECIAL MASTER HASTINGS: You have a nice,
14 soft voice.

15 THE WITNESS: No, no.

16 SPECIAL MASTER HASTINGS: You just need to
17 speak up as best you can.

18 THE WITNESS: I know it's a problem.

19 SPECIAL MASTER HASTINGS: And maybe perhaps
20 going a bit slower would make it easier to understand
21 as well.

22 THE WITNESS: Okay. Okay.

23 BY MS. RICCIARDELLA:

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

1 A Right. I went to medical school from 1971
2 to 1978.

3 SPECIAL MASTER VOWELL: Doctor, the mic
4 you're speaking into is the court reporter's mic,
5 which is very important, but the one you have your
6 slides on top of, the flat mic there, is the one that
7 actually amplifies for us here in the building.

8 THE WITNESS: This one? Okay. Thank you.
9 So I have three mics.

10 MS. RICCIARDELLA: We're high tech here.

11 THE WITNESS: I'm wired.

12 SPECIAL MASTER HASTINGS: All right. Thank
13 you, Doctor.

14 BY MS. RICCIARDELLA:

15 Q So you have a medical degree, Doctor, is
16 that correct?

17 A Yes, that's correct.

18 Q And you have a Master's certificate in
19 Biostatistics Methods in Human Physiology, is that
20 correct?

21 A Yes.

22 Q Following medical school, where did you do
23 your residence?

24 A I did my residency in psychiatry at the
25 University of Paris from 1977 to 1982 I think. Yes.

1 Q And in what field did you do your residency?

2 A I did train in general psychiatry and went
3 on to do a specialization in child and adolescent
4 psychiatry.

5 Q When did you start specializing in child
6 psychiatry?

7 A I think I made that choice in 1978 or 1979.
8 No. 1979.

9 Q And why did you decide to specialize in
10 child psychiatry?

11 A Because I had an interest in the childhood
12 antecedence of psychiatric disorders in adult life and
13 then also a strong interest in neurodevelopmental
14 disorders.

15 Q Doctor, what certifications do you hold in
16 your field?

17 A I have a medical degree, and I have full
18 training in child and adolescent psychiatry. I'm the
19 equivalent of board-certified in child and adolescent
20 psychiatry in the French system.

21 Q Is that the highest certification in your
22 field?

23 A Yes.

24 Q Your CV, Doctor, mentions that you had some
25 military duty. What did that entail?

1 A It entailed one year of my life and going
2 into the Army. I was stationed in an Army base in the
3 Caribbean Islands, the French Caribbean Islands, where
4 I was the psychiatrist on the base. I was the
5 consultation for the military staff, and I was also
6 screening the local youth populations to go out to the
7 Army. I was sent on various missions to Guyana and
8 other places.

9 Q Doctor, how long have you been working in
10 the area of childhood pervasive developmental
11 disorders and specifically autism?

12 A I think about 22 or 23 years, 22 years
13 probably.

14 Q And what training have you had in
15 epidemiology?

16 A I did Master certificates when I was a
17 medical student. I also was engaged in various
18 research projects between 1974 and 1981 I think. For
19 instance, I ran a multicentric randomized clinical
20 trial from the conception of the study to the analysis
21 of the data, so I learned and honed a lot of research
22 skills.

23 Then I went on to do a summer epidemiology
24 training program in 1986 with Professor Ken Rothman,
25 who was a well-known American epidemiologist. That

1 was in Massachusetts. Then I also attended several
2 classes on biostatistics. I went to spend a summer in
3 Ann Arbor, Michigan, to learn skills about all these
4 alternatives and other kinds of analytical skills.

5 Q And when did you begin your epidemiological
6 research?

7 A My own?

8 Q Correct.

9 A In 1985, that was when I decided actually to
10 embrace a regional study after my term was finished.
11 I was still doing clinical work but decided to develop
12 empirical studies of child psychiatric disorders in my
13 country. My approach was to develop the first
14 epidemiological study of child psychiatric disorders.
15 Not autism, just the range of psychiatric disorders,
16 emotional disorders, disruptive disorders, in a large,
17 population-based survey which I did in France and
18 started that in 1985 through 1989.

19 Q Now, Doctor, in 1989, were you recruited as
20 a tenured research scientist at INSERM?

21 A Yes.

22 Q What is INSERM?

23 A INSERM is the Institute National de la Santé
24 et de la Recherche Médicale, which is the French
25 institute which carries most of the biomedical

1 research in France. It's an equivalent of what is MRC
2 in England or what is NIH in the U.S.

3 Q Okay. And how long did you hold your
4 position as a research scientist at INSERM?

5 A I was fully employed up to the time I moved
6 in England, but I'm still actually part of it. I'm
7 detached from their active staff, but I'm still a
8 member of this institute on paper.

9 Q Doctor, in 1993, were you offered a position
10 at Maudsley Hospital and Institute of Psychiatry in
11 London?

12 A Right. Correct.

13 Q What is Maudsley Hospital and Institute of
14 Psychiatry?

15 A It's a quite unique psychiatric institution.
16 It's a large psychiatric hospital which is located in
17 South London and has a very strong reputation in terms
18 of the clinical services which are available.

19 Historically in the U.K., it has played an
20 important role for promoting research and academic
21 development in the field of psychiatry, both child and
22 adult, from the genes to the psychosocial environment.

23 It's really the place where most of British
24 psychiatry research has been coming out, and it's also
25 a place where many scholars worldwide have been

1 trained or have spent sabbatical. And the Institute
2 of Psychiatry is the academic center which is attached
3 to this hospital.

4 Q And did you work with Professor Michael
5 Rutter while you were there?

6 A Yes.

7 Q Who is Michael Rutter?

8 A Professor Michael Rutter is probably best
9 described as the founder of child psychiatry as a
10 scientific discipline. He conducted a very
11 influential study in the field of child psychiatry
12 which ranged from the first epidemiological studies in
13 the Isle of Wight in the U.K. in the late 1960s, and
14 he has also been a very important researcher in the
15 field of autism. So he's done sort of twin studies on
16 autism I think as early as 1968 or 1969.

17 Q Doctor, what position did you hold at
18 Maudsley Hospital and Institute of Psychiatry?

19 A When I was appointed there, I was appointed
20 as a senior lecturer, which is a university position.
21 My appointment was at the Institute of Psychiatry,
22 which was a university appointment. Senior lecturer
23 is one of the high positions that you can have. And
24 then I had a clinical appointment at Maudsley, which
25 was my consistent appointment, my hospital

1 appointment.

2 Q Doctor, your CV also states that you were a
3 reader in epidemiology child psychiatry at the
4 University of London. What does that mean? We don't
5 have that here.

6 A This is unique to the British system. When
7 they promote people from senior lecturer, you can
8 become a chair, a full professor, but often
9 universities have a limited number of chairs, so they
10 have this mechanism by which someone with a chair kind
11 of a level is given a position which is called reader.

12 A readership is maybe a recognition of the
13 particular academic accomplishments in a particular
14 field by someone. So it's like being a chairman
15 without the chair, and it's recognition of your
16 gaining excellence in that field.

17 Q Doctor, you're currently a full Professor of
18 Psychiatry at McGill University, is that correct?

19 A Yes.

20 Q And are you head of the Division of Child
21 and Adolescent Psychiatry there?

22 A Yes.

23 Q And you're also head of the Autism Spectrum
24 Program at the Montreal Children's Hospital?

25 A Yes. Correct.

1 Q How long have you been a full Professor of
2 Medicine?

3 A Since 1993.

4 Q 1983?

5 A 1993.

6 Q 1993. Okay. And how long have you been at
7 McGill?

8 A Since 2001, so about six years.

9 Q Your CV also states that you're the Canada
10 Research Chair in Child Psychiatry. What does that
11 mean?

12 A The Canada Research Chair Program is a
13 federal program in Canada which was established in
14 2000. The goal of this program was that the federal
15 government would provide funding, substantial funding,
16 to various universities in Canada to attract in Canada
17 people with an international profile of academic
18 excellence is how it was set up. That's the mechanism
19 which was used by McGill to recruit me into serving
20 with them.

21 Q Doctor, are you associated with any
22 hospital?

23 A Yes. I work at the Montreal Children's
24 Hospital, which is the pediatric hospital of McGill
25 University.

1 Q Okay. And do you hold any teaching
2 positions in your specialty?

3 A I do, yes. I do teach as part of my regular
4 duties.

5 Q You're a full professor. I guess so.

6 A Yes.

7 Q Who do you teach?

8 A I teach a range of different people, firstly
9 the residents in psychiatry. I teach child psychiatry
10 to them. I also teach residents in pediatrics or
11 residents in neurology which audit into my program. I
12 do teach medical students. And I do teach in a number
13 of settings community pediatricians, general
14 practitioners, family doctors and mental health
15 professionals in general.

16 Q Do you teach epidemiology methods in child
17 psychiatry research?

18 A Yes.

19 Q Does that include the epidemiologic methods
20 of studying children with autism?

21 A Yes. I started with that, but I teach
22 broader.

23 Q How long have you been teaching?

24 A I think I started to teach in 1985 or 1986.

25 Q And do you also teach child psychiatry?

1 A Yes.

2 Q Okay. Now your CV states that you're an
3 organizer and teacher of a summer school program of
4 the Autism Research Training Program. What is that?

5 A Oh, this is a special grant that I secured
6 in 2003. It's a six-year grant which it's a strategic
7 training grant in Canada which is funded by CHR, and
8 the goal is really to boost research capacity in
9 Canada by attracting in the field of autism research
10 young, promising fellows at the different degrees in
11 their career, Master degrees, Ph.D. or postdoc.

12 I have assembled a group of labs in eight
13 Canadian universities where we train these fellows.
14 We give them fellowships. And as a part of this
15 particular effort, we have set up a summer school in
16 autism which we have run for three or four years now
17 at McGill in the summer where they all come, the
18 faculty, and we train them quite intensively to autism
19 research in particular.

20 Q Doctor, do you lecture to professional
21 groups and organizations concerning childhood
22 pervasive developmental disorders?

23 A Yes, I do. Yes, I do.

24 Q Do you lecture worldwide?

25 A Yes, I do that.

1 Q Approximately how many times a month do you
2 lecture worldwide?

3 A How many times?

4 Q Per month.

5 A Per month? I don't know. It's hard. I
6 think on average probably 10, 12 lectures about every
7 year, so about one a month.

8 Q Do you devote time to family-based
9 associations pertaining to autism?

10 A Yes. Since I have been in that field, I
11 have been very involved with family associations in
12 France initially but then in the U.K. In Europe,
13 there is an organization called Autism Europe, which
14 is a federation of family associations which organize
15 every three or four years a conference. I have been
16 consistently involved in the scientific planning of
17 this conference with them, and I'm a regular guest
18 speaker to their conferences.

19 Q And do you have a connection with an
20 organization called Autism Speaks?

21 A Yes. Autism Speaks provides some funding to
22 the training grant which I just mentioned before.
23 They are in partnership with CHR, which is the NIH
24 equivalent in Canada, so they fund some of my
25 research. But they also are currently actually

1 funding an epidemiological study that I am carrying
2 out in South Korea with American colleagues.

3 I am also involved with them in terms of
4 lecturing. They're organizing a big event in the next
5 few weeks in Mexico to boost advocacy and awareness
6 about autism in Central America and South America. So
7 they are organizing a large conference, and I am a
8 speaker there.

9 I'm also involved as a psychiatric advisor.
10 Autism Speaks is funding a large genetic project
11 which I'm sure Dr. Cook will mention later. They have
12 set up a scientific advisory committee, and I'm part
13 of that. I've been reviewing as part of their grants
14 review board once or twice.

15 Q Doctor, I'd like to talk about your actual
16 experience as a child psychiatrist and epidemiologist
17 over the past 29 years specifically as it relates to
18 the disorder of autism. Have you ever diagnosed and
19 treated a patient with autism?

20 A Yes, I do that.

21 Q How many times?

22 A Oh, it's hard to know. I've probably seen
23 like 100 or I would say 2,000 maybe children with
24 autism.

25 Q Do you currently have a clinical practice?

1 A I do. I do see patients quite regularly.

2 Q And as part of that clinical practice, do
3 you diagnose and treat children with autism?

4 A Yes.

5 Q How many per year approximately?

6 A I think currently in our clinic, we probably
7 see about 350 new diagnosed cases per year, and I
8 probably out of these see half of them about. It's
9 hard to say.

10 Q And currently how many autistic patients are
11 you following?

12 A That I follow? Probably I would say 200. I
13 do see patients for initial assessments. I do follow
14 up on them. I also am running a psychopharmacology
15 clinic, which is to help for the handling of difficult
16 behavior in children who aren't diagnosed but are
17 older and where behavior interventions have failed.
18 We sometimes use mitigation. I'm one of the medical
19 leaders of that clinic, which is part of my autism
20 program.

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

23 A Well, all the time because they are present
24 at all assessments. We work with families and parents
25 very closely of course.

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

3 A Yes.

4 Q Approximately how many?

5 A I've been involved in a number of studies,
6 probably eight or 10 now in several countries.

7 Q Okay. And, Doctor, you've published over
8 160 articles related to childhood pervasive
9 developmental and behavioral disorders, is that
10 correct?

11 A Yes.

12 Q And are all those articles peer-reviewed?

13 A Yes.

14 Q In addition, you've published 34 book
15 chapters pertaining to childhood psychiatric and
16 developmental disorders, including an epidemiologic
17 study of autism, is that correct?

18 A Yes.

19 SPECIAL MASTER HASTINGS: Rather than nod,
20 you need to say yes.

21 MS. RICCIARDELLA: It has to be audible,
22 your response.

23 THE WITNESS: Oh, yes. Sorry. Sorry. I
24 said yes. I didn't count them, but you did.

25 MS. RICCIARDELLA: I did.

1 BY MS. RICCIARDELLA:

2 Q And you currently serve on the Editorial
3 Advisory Board of the *Journal of Child Psychology and*
4 *Psychiatry*, is that correct?

5 A Yes.

6 Q What does it mean to be on an editorial
7 advisory board?

8 A Well, it means that you receive a fair
9 amount of submissions, articles that are submitted to
10 the journal, that you are asked to review carefully.
11 I've been on that editorial board for, I don't know,
12 probably 15 years. I was asked actually to be the
13 editor of the journal, but I refused to do it because
14 the task is enormous. But I'm involved. I do review
15 a number of journals and this one in particular quite
16 regularly.

17 Q And your CV states that from 1994 to 2003,
18 you were the associate editor of the *Journal of Autism*
19 *and Developmental Disorders*, also known as *JADD*.

20 A Yes.

21 Q What is *JADD*?

22 A *JADD* is one of the leading autism journals.
23 It has been around for I don't know how many years,
24 but like 50 or 60 years. It actually changed its name
25 in 1978. It was previously the *Journal of Autism and*

1 *Childhood Schizophrenia*, and then it switched to
2 *Journal of Autism and Developmental Disorders* when the
3 concepts in the field evolved. So it's one of the
4 most widely read journals in the field of autism.

5 Q And are you also a reviewer for other
6 journals?

7 A Yes. I do review all the time.

8 Q Doctor, there's been a lot of discussion in
9 this case about an organization called IMFAR. What is
10 IMFAR?

11 A IMFAR stands for International Meeting For
12 Autism Research, and now it's actually combined with a
13 society which is called INSAR, which is International
14 Society for Autism Research, so IMFAR or INSAR. IMFAR
15 is the name of the meeting. INSAR is the name of the
16 scientific society.

17 IMFAR was set up in 2001. It was on the
18 initiative of different scholars in the U.S. and
19 Britain and also with the help I think of some family
20 associations or some organizations like the Mind
21 Institute. The idea was up to that point there was no
22 autism meeting which was specific to autism, so people
23 like me or other researchers were going to different
24 meetings to publish their findings. So geneticists
25 would go to genetic meetings. Neurologists would go

1 to neurological meetings.

2 There was no meeting which would focus on
3 autism from a range of different perspectives or with
4 much specificity, and so IMFAR was really set up to
5 address that need and to provide the multidisciplinary
6 research meeting on autism. It's a very successful
7 meeting.

8 Q And did you participate in the first
9 conference, the first meeting of IMFAR in 2001?

10 A Yes.

11 Q How did you participate?

12 A I was one of the invited guest speakers
13 alongside with Dr. Bailey and Dr. Lord on genetics.

14 Q Are you currently a member of IMFAR?

15 A Yes.

16 Q And how have you participated in IMFAR since
17 its initial conference in 2001?

18 A I've been involved in the organization in
19 different ways. I was initially on the Membership
20 Committee trying to set up rules and regulations to
21 develop the association of IMFAR, which is now formed.

22 More recently I was part of the publication
23 committee, which was set to evaluate whether or not we
24 should develop a new scientific journal of autism,
25 which we finally decided to launch. So soon I think

1 there will be a new journal which will be attached to
2 the scientific organization.

3 Q Doctor, there's also been discussion in this
4 case about a poster presentation that was presented at
5 the 2006 IMFAR conference. You were president of the
6 Scientific Committee at the 2006 IMFAR conference, is
7 that correct?

8 A Yes. Yes, I was.

9 Q What does it mean to be president of the
10 Scientific Committee?

11 A It means that you do the work to organize
12 the concern. It means that I was the scientific
13 organizer of the concerns they had to select people to
14 have a Scientific Committee, which I did. I selected
15 people to work with me, and then we had to receive
16 applications for potential presenters for all
17 communications or poster communications.

18 Q And how are posters selected for
19 presentation at an IMFAR conference?

20 A Well, we select them. The process is that
21 people post their submissions on the website, and then
22 I look at it from each poster application or each
23 communication application. Two, sometimes three,
24 independent reviewers give their opinions on whether
25 or not it would be accepted.

1 Then I reviewed all the opinions of these
2 reviewers and made a final decision about accepting or
3 rejecting this particular application, and then I
4 organize the program, who speaks and who presents
5 their poster. It's quite a number of hours spent.

6 Q Doctor, how often do you do consulting work
7 in lawsuits?

8 A Very rarely.

9 Q And the lawsuits you've consulted on, what
10 kind of cases have those been?

11 A Cases that were submitted involving links
12 between vaccines and autism.

13 Q And have you consulted for the
14 pharmaceutical manufacturers?

15 A Yes.

16 Q Do you recall consulting for the
17 pharmaceutical manufacturers in a case known as
18 Easter?

19 A Yes.

20 Q And you testified at what's called a Daubert
21 hearing in the Easter case, correct?

22 A Yes, that's correct. That's the one time I
23 did participate in such litigation.

24 Q And other than your testimony in the Easter
25 case at the Daubert hearing and your testimony today

1 here in Court, have you ever testified in another
2 Court?

3 A No, I have not testified otherwise.

4 Q Now, Doctor, your CV states that you were
5 the advisor to the Chief Medical Officer in the United
6 Kingdom concerning the controversy about MMR and
7 autism. First of all, is the Chief Medical Officer a
8 government position, a British Government position?

9 A Yes. I think it's probably comparable to
10 the General Surgeon in the U.S.

11 Q The General Surgeon?

12 A Yes, I think so. It's someone who really is
13 there to look at public health issues and represent
14 the Department of Health. So when the initial
15 publication of Dr. Wakefield was released first, it
16 was involving a MRC review of Dr. Wakefield's work.

17 The Chief Medical Officer started to be
18 concerned. He wanted to review the evidence about
19 autism, the epidemiology, what we knew about the link
20 between vaccines, so he set up an advisory committee
21 which comprised people who knew about autism. So I
22 had colleagues, not just clinicians but who knew well
23 autism and clinical presentation. I was there because
24 I was one of the clinical autism experts but also
25 based on my knowledge and experience in epidemiology

1 of autism, so that's what it was.

2 Q Were you paid?

3 A No. No, I was not. It had nothing to do
4 with the litigation in the U.K. It was just a
5 conservative committee, which probably met, I don't
6 recall now, probably twice, maybe three times.

7 Q Now, Doctor, the law of our Court requires
8 you to give your opinion to a reasonable degree of
9 medical probability. As you testify today, if you
10 cannot give your opinion to a reasonable degree of
11 medical probability, you'll let us know. Is that
12 okay?

13 A Yes.

14 Q Doctor, did Michelle's receipt of
15 thimerosal-containing vaccine in the MMR vaccine cause
16 or contribute to her autism?

17 A No.

18 Q Now, before we discuss the specifics about
19 Michelle Cedillo's case, I'd like to discuss generally
20 what autistic spectrum disorder is. I believe that
21 you have some slides to help illustrate your comments.

22 A Yes. Yes.

23 SPECIAL MASTER HASTINGS: To both the
24 attorney and the witness, as we go through these, it's
25 helpful for us to make our record that as you move

1 from one to the next you say the number of the slide
2 you're on.

3 MS. RICCIARDELLA: Certainly.

4 THE WITNESS: Okay.

5 BY MS. RICCIARDELLA:

6 Q Doctor, is the term autistic spectrum
7 disorder the same thing as pervasive developmental
8 disorder?

9 A Yes. As the slide indicates, the pervasive
10 developmental disorder is really a class of diagnoses
11 which we'll discuss later, but it's a group of
12 conditions, and it's sometimes referred to as PDDs but
13 also referred to as autism spectrum disorder. These
14 are two equivalent terms, and the terminology is
15 somewhat confusing.

16 MS. RICCIARDELLA: And for the record, the
17 Doctor is referring to Slide 1.

18 SPECIAL MASTER HASTINGS: Right.

19 THE WITNESS: It's Slide 1, yes. The way
20 they are currently defined and conceptualized is that
21 these are for children who develop abnormally in three
22 domains of their development, and those three domains
23 involve the language but more broadly the way the
24 child communicates with or without language.

25 Secondly, they have abnormalities in the way

1 they interact with other persons, and thirdly, they
2 have abnormalities in the way their play skills
3 develop or their behaviors or their style of behavior
4 which tends to be repetitive and rigid. So we seek
5 for evidence of abnormalities in the development of
6 these three domains in a child, and it has to be
7 evident before the age of three.

8 As you can see on that slide, the emphasis
9 now is on qualitative development of abnormalities.
10 It's important to understand that because in the past
11 when Tanner described autism, certain epidemiology
12 studies were looking at children who were not only
13 very different in terms of their development, but they
14 were often very delayed. So they were children who
15 had cognitive deficits, had no language, had no eye
16 contact, and the delay in the development was a major
17 defining feature of these early descriptions.

18 As we moved along, we started to recognize
19 that in fact the delay was part of the definition in
20 some cases but not always and that you could see
21 abnormalities in the development of children without
22 to really require that there would be a delay so that
23 you could have, for instance, fully developed language
24 in a child, but it was important that it was not using
25 language to communicate in a reciprocal way.

1 So eye contact, which is supposed to be
2 constantly lacking, could be present, but the quality
3 of the eye contact would be different, so the child
4 would stare at people or would not regulate sufficient
5 interaction with very subtle change in the eye gaze.

6 BY MS. RICCIARDELLA:

7 Q Doctor?

8 A Yes?

9 Q Go ahead. Go ahead. I didn't mean to
10 interrupt you. Does your Slide 2 talk about these
11 three domains?

12 A Okay. Yes. So the idea is that in terms of
13 the current diagnostic indications, we really look at
14 impairments or deficits in these three domains, social
15 interactions, communication and language and
16 repetitive behavior, but what we know now is that the
17 symptoms, which is the second level that you can see
18 on the slide, the symptoms which are mapping these
19 deficits can be very different, and you will see that
20 in a moment.

21 It's important to recognize that different
22 children who have the same diagnosis would present in
23 very different ways. They would not look at all the
24 same if they are together, although they have the same
25 diagnosis at the same age.

1 Secondly, within the same child, if you
2 follow a child from age 3 to 5 to 8, the symptoms will
3 really be very different. There would be a change in
4 the symptomology, in the profile of symptoms, as the
5 child develops, so that makes the understanding of the
6 diagnosis and the evaluation quite difficult sometimes
7 to understand.

8 So we look for the symptoms when we evaluate
9 children, and then when we elicit these symptoms in
10 our assessments, we then require that the child have
11 symptoms indicating a social deficit and symptoms
12 indicating a communication deficit and symptoms
13 indicative of repetitive behavior. And that's the
14 combination of these three sets of symptoms which
15 define the presence of a PDD or an ASD.

16 Q Doctor, what are the particular symptoms
17 that you look for to diagnose a child with an ASD?

18 A Yes. So that's the slide that illustrates
19 the kinds of symptoms that we would see.

20 Q And for the record, Doctor, you're referring
21 to Slide 3 now?

22 A Yes, which really maps the domain of
23 abnormalities in language and communication.

24 If we can just take the time to discuss a
25 few of these, particularly of the presenting young

1 infants, for instance, often there is language delay.

2 There is no babbling. There can be no babbling in a

3 young infant or the babbling can be very limited.

4 For instance, you could recognize that the

5 amount of babbling is reduced or the quality of the

6 babble is also altered. There would be very little

7 babbling not directed to communicate. It would be

8 self-directed, not used with a communicative intent.

9 Young babies when they babble are usually

10 communicating in sort of a toing and froing fashion,

11 and often in autism, the babble would be already quite

12 different. So we look at different qualities of the

13 babbling.

14 What is important as well is when the child

15 has no language or is delayed in his language

16 development. What the child usually will do who has

17 just language delay is they would use gestures to

18 communicate to compensate for their lack of language.

19 In autism, we see precisely that it's not

20 only the language which is lacking, but it's also the

21 capacity to communicate with other beings. So the

22 lack of gestures would be something which is critical

23 to evaluate the communication deficits in autism and

24 to differentiate them from language disorder, for

25 instance.

1 We also, for instance, look at particular
2 gestures like pointing. Pointing is an important
3 aspect in the development, and to illustrate how it
4 can be sometimes difficult to understand, we have done
5 studies which now show that autistic children can
6 point.

7 The type of pointing that they use is what
8 we call protoimperative, which they can point at
9 objects that they want or need, so that kind of
10 pointing they would do. What they do not do is
11 pointing at a distance to show something, to share an
12 interest when someone is in the room. Now this is a
13 different type of pointing.

14 That distinction is not something that we
15 carry with us as laypersons and actually can make it
16 for people that will not make the distinction for
17 themselves. Parents will often say, well, yes, my
18 child points. Unless you look at the behavior, you
19 will not know if it's protodeclarative pointing or
20 protoimperative. We try to make the distinction, but
21 it's very critical to the development of autistic
22 children.

23 There are other gestures that young children
24 do like nodding, shaking their heads to mean yes or
25 no, waving bye-bye. All these gestures are developing

1 at around age 8 to 12 months, and their absence can be
2 quite significant for the evaluation of these
3 children.

4 You can see as you go down the slide the
5 degree of skills increase, and you can have sometimes
6 fully developed language skills in a high functioning
7 child, an Asperger child or a functioning adult, but
8 there will be different types of abnormalities in the
9 communication. There will be little understanding or
10 the conversation will not flow back and forth in a
11 sort of normal way. So as you evolve and the child
12 grows, the language deficits will take a different
13 form.

14 If I can have the next slide? This is the
15 second domain of abnormalities, which is the social
16 interactions.

17 Q And you're referring to Slide 4.

18 A Yes. Again looking at the first four or
19 five symptoms, these are symptoms that you would be
20 typically identifying in young children. So the eye
21 gaze would be poor. There could be lack of eye gaze
22 or an eye gaze which is not really used flexibly to
23 regulate the interaction.

24 Social smiling is often lacking. Social
25 smiling is a response that we all have. When we

1 approach, we smile socially, or when you smile at
2 someone, people smile back. It's kind of a
3 preprogrammed response in the brain. That's often
4 lacking in autism.

5 A very typical behavior which is sometimes
6 lacking or often lacking in children with autism is
7 the response to name. So when you call someone, you
8 call a child, usually you have an orientation to the
9 name being called. The child turns his head and looks
10 at the person who called his name. This is something
11 which is often critically lacking in autism.

12 For instance, in a young child, you could
13 see as well a reduction of the capacity to display a
14 normal range of facial expression and to share affects
15 with other persons as part of the interaction.

16 Q You mentioned a third domain as repetitive
17 behavior?

18 A Yes. Yes.

19 Q What symptoms do you look for in this third
20 domain? I'm referring to Slide 6.

21 A There are different types of --

22 Q Slide 5. Excuse me. Slide 5.

23 A Yes. Again, there will be different types
24 of symptoms, and there would be some additions to the
25 levels of development.

1 One typical sign is a certain type of a
2 stereotyped movement that young children can do
3 sometimes or children who are like toddlers where they
4 would move their hands in different particular ways.

5 A typical stereotypic movement is when they
6 move their fingers individually like that. It's very
7 highly specific to autism. Often they will do some
8 clapping or flapping of their hands, which is quite
9 intense and goes beyond the sort of normal overflow
10 movement that we see in normal infants or toddlers.

11 We can have also odd ways to manipulate
12 objects. When the child is 2 or 3, there is usually a
13 lack of imaginary play or lack of pretend play that
14 they would use toys for nonfunctional uses. They
15 would line up toys or do things which are equivalent.

16 One thing which is often seen in addition to
17 developmental levels is unusual interests, so they
18 have fixations for particular activities. They might
19 seem to be normal activities, but what makes this
20 affixation unusual is that they are always the same.
21 They exclude social activities. They do not progress
22 over time.

23 The child can be, for instance, engrossed
24 into like looking at fans on a ceiling. It would be
25 that sort. It can be normal in a normal child to look

1 at fans because it's interesting for a few seconds,
2 but what is unusual is that they would spend 30
3 minutes and they would be angry if you tried to get
4 them to do other things, or they would be going after
5 pipes or flushing toilets or looking at washing
6 machines on and on and on.

7 That can last for very, very, very long
8 periods of time, and it really excludes other normal
9 activities that you would like the child to engage in
10 as part of his normal development. There are other
11 kinds of things too which are of a similar nature like
12 that.

13 Q Do clinicians such as yourself have a method
14 for diagnosing and assessing autism or ASD in general?

15 A Yes.

16 Q And you're on Slide 6?

17 A If one is reminded of the slide, we have
18 these domains where we need to identify deficits. Our
19 task when we do an assessment is to elicit the
20 symptoms in that child which are mapping these
21 deficits in the development.

22 For that, there are different ways to do it.
23 You can do just a clinical assessment. The clinical
24 assessments are often limited because they are viable,
25 so we tend to use now our field different tools. One

1 tool, which is the Childhood Autism Rating Scale, has
2 been used for many years. It's a clinician-rated
3 instrument which allows one to derive a score which is
4 indicative of autism.

5 The most recent instruments are the ADI and
6 the ADOS. These are standardized measures which are
7 used now worldwide both in clinical settings and in
8 research settings, and I put them there because a lot
9 of them are published with the research as diagnostic
10 tools.

11 The ADI is a developmental interview which
12 lasts two or three hours, which is an interview with
13 the caregiver, usually the mother, to elicit again the
14 symptoms of autism both currently and in the early
15 development of the child.

16 Then it's combined with the other of the
17 two, which is called the ADOS, which is a direct
18 examination which is standardized. By that, we mean
19 that we do the same things with different children at
20 different centers, and we create really context and
21 precis to elicit social or communicative behaviors in
22 the child to see if they communicate or interact
23 appropriately. Unless you do that in some children
24 who have subtle difficulties, you would probably miss
25 the difficulties.

1 So there has been a lot of progress since
2 the late 1980s when the first fashions of these two
3 instruments were used. It's important to know that
4 everybody at every Asperger center currently uses the
5 diagnostic measures, again both for research reasons
6 but also for clinical reasons.

7 With that, it has really helped to achieve a
8 high degree of interclinician agreement for autism,
9 PDD and different subcategories. It's one area of
10 psychiatry or child psychiatry where the agreement is
11 the highest in terms of the presence or absence of the
12 PDD. There is very strong consensus of what it is and
13 high reliability now and clinical conclusion when we
14 use these tools.

15 Q Doctor, when you talk about ASDs, what are
16 the ASDs?

17 A PDD and ASD are umbrella terms for a class
18 of different diagnoses, and when we do assessments, we
19 usually start with asking the question does the child
20 meet the full criteria for autistic results. That's
21 how we go throughout our diagnostic decision tree.

22 If the child meets the criteria for autistic
23 disorder, which I will describe in a minute, in other
24 words, he has sufficient symptoms indicating deficit
25 in the three domains, then the diagnosis is autistic

1 disorder. If he does not, then we look at other kinds
2 of diagnoses.

3 Atypical autism, which is also often
4 commonly referred as PDD-NOS. PDD-NOS stands for
5 pervasive developmental disorder not otherwise
6 specified, which is a terminology that nobody likes
7 very much, but we employ it.

8 It's really for where we have not the full
9 set of symptoms, the full complement. They are
10 missing the criteria for autistic disorder by usually
11 a small margin. There are subthreshold clinical
12 presentations or the age of recognition by parents
13 might be beyond the age of 3, so we cannot apply our
14 age of onset criteria, but they are on the same kind
15 of spectrum but often less severely afflicted.

16 The third category is Asperger syndrome, and
17 this is for children who have basically the same
18 impairments that you see in autism except that their
19 language develops within normal limits. So these are
20 children by age 2 they have multiple words. They
21 start to combine words into sentences, and by age 3,
22 their freelance language, if they can talk, is often
23 good. Their conversational skills are often impaired,
24 but this is subtle. What it means is the development
25 of the language by and large is normal and does not

1 concern the parents during these first years of life.

2 The second characteristic which is currently
3 included in the diagnosis is that by definition it is
4 required that this child would not have mental
5 retardation. So on testing, their intellectual
6 quotient or IQ must be in the normal range.

7 It must be said that some children with
8 autistic disorder also have a normal IQ, but many of
9 them have actually mental retardation too. This does
10 not differentiate entirely Asperger from autistic
11 disorder, but Asperger by definition, they all have
12 normal IQ.

13 Then there are two other subtypes. The
14 fourth one, which is childhood disintegrative
15 disorder, is very rare. It's like 100 times rarer
16 than autism, to describe a clinical picture, which is
17 like autism, which is very severe. As I said, there
18 is usually mental retardation, but the way it develops
19 in the development of the child is unusual.

20 In those instances, the development of the
21 child is really unambiguously normal up to at least
22 the age of 2 and often up to the age of 3. So these
23 are children who speak, who interact and play, and
24 then within weeks or sometimes months, weeks often,
25 they start to deteriorate, lose their skills in a very

1 dramatic fashion, and the end point is the clinical
2 picture of severe autism.

3 Literally it's quite dramatic, quite
4 distressing, but very rare. I've seen a few cases in
5 my life, but it's not very common. We don't know if
6 this a different etiology in the form of autism or an
7 additional developmental disorder.

8 Then the last one is Rett syndrome -- this
9 is really for girls -- which usually develops normally
10 up to a certain age, up the age of 6, 8, 10, sometimes
11 later. They develop absolutely normally and then
12 suddenly there is the onset of neurological signs.
13 They develop stereotypic movements, particularly a
14 ranking stereotypic in the midline, and then there are
15 also neurology concerns. So the head circumference
16 disintegrates. They have at the end microcephaly, and
17 then they develop neurological signs.

18 This syndrome now is mostly studied in a
19 different way. A gene for it has been found in 1999.
20 The interest of mentioning that today is that it's a
21 disorder for which we know that there is a genetic
22 acuity which is absolutely established. The MECP2
23 gene is responsible for that syndrome, but it's
24 associated with a period of normal development and
25 then there is a dramatic loss of skills.

1 So it's important to remember in terms of
2 discussing regression because it's an example of
3 regression occurring after a period of normal
4 development, and yet the determination of the disorder
5 is entirely genetic.

6 Q So those are the five ASDs. What is meant
7 by the term *DSM-IV*? What is *DSM-IV*?

8 A *DSM-IV* is the *Diagnostic and Statistical*
9 *Manual*. It has several editions. The current edition
10 is the fourth edition, which was released in 1994.
11 It's a diagnostic system which provides diagnostic
12 categories and diagnostic criteria for the whole of
13 psychiatry. So you have various chapters for adult
14 disorders, substance abuse disorders. And there are
15 chapters for childhood disorders and one chapter which
16 deals particularly with developmental disorders,
17 including autism.

18 Q Does the United States use the *DSM-IV*?

19 A Yes. It's the -- which is in use in the
20 U.S. and in North America.

21 Q And what are the diagnostic criteria for
22 autistic disorders specifically in the *DSM-IV*? And I
23 know you're referring to Slide 8.

24 A These are the diagnostic criteria. So when
25 we do an assessment, we try to observe symptoms, and

1 when we have observed enough symptoms, then we see if
2 the child meets these criteria. These criteria, there
3 are 12 criteria. They're organized in three sections,
4 which is social interactions, communications and
5 repetitive behavior, and in each of these sections, we
6 have four types of symptoms.

7 After an assessment, we would see the child
8 is missing criteria for A and B in a section for
9 social interaction, and then we turn the page. We
10 look at the communication and the language section.

11 Q And you're referring to Slide 9?

12 A Yes. Then there are also four symptoms that
13 could be endorsed here, and then the third section has
14 also four symptoms.

15 Q Slide 10.

16 A So there was a total of 12 symptoms, and to
17 meet the criteria for autistic disorder, the child
18 must have six symptoms out of the 12. Their
19 repetition must be such that there are at least two
20 symptoms in the social domain, one in the
21 communication domain and at least one in the
22 repetitive domain.

23 These diagnostic criteria have been tested
24 empirically. They are those which provided the best
25 combination of sensitivity and specificity in a large

1 multicountry, multisite study which was conducted
2 between 1991 and 1993 to look at the best algorithm,
3 which would be the most performing in clinical
4 settings.

5 Q And for the record, you've been referring to
6 Slides 8 through 10.

7 A I'm sorry?

8 Q I'm just making the record. You've been
9 referring to Slides 8 through 10.

10 A Yes.

11 Q Doctor, what is *ICD-10*? Is that an
12 equivalent to *DSM-IV*?

13 A Yes and no. *ICD-10* stands for *International*
14 *Certification of Disease*. It's the tenth edition.
15 There's been several editions over the years. The
16 last one was 1978, ninth edition.

17 *ICD-10* is actually another system which
18 provides categories for all the whole of medicine. So
19 it's a system which you use in many parts of the
20 world, especially for administration of hospital
21 statistics to report morbidity and other statistics
22 because it provides a way to code any kind of medical
23 condition. And within all these medical conditions,
24 there is a whole section on psychiatry, which is the
25 section which is like the *DSM-IV* with some

1 evaluations.

2 Q And were you part of the group that helped
3 develop the criteria for both *ICD-10* and the *DSM-IV*?

4 A Yes. There was a task force which was
5 asserted in 1990 to 1991, and I was a representative
6 of WHO with Michael Rutter, and we met with the
7 equivalent from the American Psychiatric Association
8 where the charter had regrouped to. We tried to make
9 diagnostic criteria more compatible across the two
10 schemes, the *DSM-IV*, which was in preparation, and the
11 *ICD-10*, which was in preparation. We met and tried to
12 make the criteria as similar as possible.

13 Q In your practice in Montreal, which criteria
14 do you use?

15 A Well, we use predominantly now *DSM-IV*.

16 Q *DSM-IV*?

17 A Before that, it was *ICD-10*. That has
18 changed.

19 Q Doctor, is autism a relatively new disorder?

20 A No. It has been described in 1943 by Tanner
21 in a very seminal paper, but in fact there is evidence
22 that autism could be found much before that.

23 There is a British scholar whose name is Uta
24 Frith who has published a book where she reviewed with
25 much detail historical accounts of particular people.

1 She described a monk in the twelfth century which most
2 certainly had autism. She also described a Scottish
3 scholar who had high functioning autism. And also
4 there was a review of an intern's work where he looked
5 at a feral child who was raised in the wilderness and
6 was recovered at school age I think. This child had
7 all the particular dramatic features of autism.

8 So there are many historical accounts of
9 autism being there before. It was not identified as
10 such. There was no name for it at the time. The
11 particular disorder which is CDD was discovered as
12 early as 1908 by Heller under a different name. And
13 in fact we have found more recently an account in the
14 Russian literature in 1926, for instance, that there
15 was a paper by Ssucharewa which in its title she talks
16 about autistic psychopathy, which was the term used
17 frequently by Asperger and Tanner.

18 So clearly before Tanner and Asperger, there
19 were accounts of these clinical presentations under a
20 name which was not very dissimilar.

21 Q Doctor, when does autism typically get
22 recognized? What age?

23 A Okay.

24 Q I'm referring to Slide 12 now.

25 A Okay. On this slide, this slide is a study

1 which is somewhat old, but it has a large number. It
2 really provides a breakdown of the age of onset in
3 autism as determined by parents when they go into
4 clinics.

5 When I say "onset," I put that in quotes
6 because actually it's a misnomer. It's clear that
7 when the first signs are seen, it's not indicative
8 that the onset of the disease is at that time.

9 Just if you'll allow me to make an analogy,
10 if someone has a cancer and the first symptom of a
11 cancer would be like, for instance, coughing blood,
12 okay, if you have lung cancer. Of course when this
13 symptom occurs in the person, it's not indicative that
14 the disease process starts now. The disease process
15 has been going on for many, many, many months and
16 sometimes years before.

17 So it's not the onset of the disease process
18 which is indicated here. It's just the age at which
19 parents start to recognize the problem, and by that, I
20 mean that it must have been going on for multiple
21 weeks or months before. We'll come back to that
22 later.

23 So when we say age of onset, it's a bit of a
24 misnomer. But on that particular study, you can see
25 that from zero to 12 months, it's only 38 percent of

1 the parents who are becoming aware before the first
2 birthday that the child's development is not quite
3 right. You can see, therefore, that over 60 percent
4 of parents in that study became aware of the
5 abnormalities in the development sometime after the
6 first birthday. And that is often what we see in our
7 clinics still now.

8 Q What symptoms do parents typically look for
9 or typically recognize as the first symptoms of an
10 abnormality?

11 A A typical story would be that the child
12 seems to develop normally. The parents do not notice
13 any particular abnormalities, but they tend to be
14 concerned often in the third semester of life or
15 fourth semester of life, and one of the first concerns
16 which is often noted by parents is the lack of
17 development of language.

18 Typically at age 15, 16, 18 months parents
19 become worried because their child is not talking yet,
20 and they can see that other children have started to
21 develop words, many words by then.

22 So in that study, the study done in the U.K.
23 where we evaluated like 80 consecutive referrals in my
24 clinic using the Autism Diagnostic Interview, you can
25 see that the concerns were noted were predominantly

1 language and speech delays and then like the social
2 difficulties in just 40 percent of the cases. The
3 main concern was in the majority of the cases the
4 language difficulties.

5 One aspect of the study to which I would
6 like to draw attention is the line which is below the
7 table where --

8 SPECIAL MASTER HASTINGS: Now, Doctor, we're
9 now on Slide 13. Go ahead.

10 THE WITNESS: Yes. In that study it says
11 like 80 percent of the parents had recognized the
12 difficulties by the second birthday, but only 30
13 percent by the first birthday. That was our data.

14 You see the mean age here at the first point
15 of concern is 19 months, and that is something which
16 when we looked at most studies published recently
17 which use the same measure, which is the ADI, come out
18 with a mean age of parents' recognition of the first
19 symptoms, which is anywhere between 14 months, 16
20 months, 18 months, 19 months. It's that sort of
21 range.

22 The point which is important to notice here
23 is that we express this in months, and there is no way
24 that when we evaluate the onset of the first symptoms
25 or the time at which parents became concerned that we

1 could date that by the day.

2 It has never been possible for us to say
3 this child became autistic on that day. It doesn't
4 occur overnight. It occurs very perversely, very
5 gradually, and then parents start to recognize the
6 difficulties sometime say between Christmas and school
7 time. It's always quite vague.

8 We work with intervals of time, and this is
9 why we express always in research when we look at this
10 variable, the only way we can really tackle it and
11 measure it is in months, never in days.

12 It was quite a remarkable feature of Dr.
13 Wakefield's research that he could date the onset of
14 symptoms in days because it's really contrary to every
15 experience of clinicians in that field.

16 I want to just show maybe the next slide,
17 which is Slide 14.

18 BY MS. RICCIARDELLA:

19 Q Is this how you evaluate a child?

20 A Yes. This is the measure I mentioned
21 before, which is the Autism Diagnostic Interview, and
22 this is Question No. 2, one of the initial questions.

23 You can see that on that diagnostic
24 interview, which is the standard diagnostic measure
25 that we use, we only ask questions in months because

1 we know by experience that we cannot date the onset of
2 symptoms in days or not even in weeks.

3 So I think it's important to bear in mind
4 that dating of the symptoms in days is not something
5 which is standard and not actually possible.

6 MS. RICCIARDELLA: And Dr. Fombonne is
7 referring to Slide 14.

8 BY MS. RICCIARDELLA:

9 Q Doctor, what is regressive autism?

10 A Okay. Regressive autism is not a diagnosis
11 first. It's a kind of a subtype. It's a clinical
12 subtype, a qualifier that's been used to index some
13 kind of trajectory in the development of children who
14 have a formal diagnosis of PDD-NOS or autistic
15 disorder.

16 So if we just look at this diagram, let's
17 assume like this is the normal development. There are
18 different types of entry into autism. The first type
19 would be children who have an early onset, and these
20 are children who you could see at age six months start
21 to be abnormal.

22 So these would be children who were not
23 babbling completely, not responsive, don't give eye
24 contact, get fixated like on the lights, don't pay
25 attention to the face of their mother, the early

1 signs, or sometimes we have -- events in the crib at
2 age eight months. It can happen. So this is an early
3 onset where the onset of autistic symptoms is seen
4 before the first birthday.

5 Then there is another group which is quite
6 the majority of them, in fact. These are children who
7 seem to develop all right up to a certain point, which
8 is like 12 months, 14 months of age, and then it's a
9 very progressive deviation of their development from
10 the normal curve.

11 It happens very slowly, but it's that the
12 child fails to acquire skills that he should acquire
13 in normal development. It's a very slow way of
14 transition that the child is not developing normally
15 as he should. This is like sometimes we call the
16 group fluctuating skill acquisition, but it's a
17 progressive onset or progressive unfolding or
18 emergence of the autistic signs.

19 Then there is a third group, which is now
20 called regressive autism. The way it's proffered here
21 is that you can see there seems to be normal
22 development up to a certain point, and here it's about
23 up to age 18 months because it's usually the age
24 between 15, 16 and 20 months of age where there is
25 this loss of skills which is reported by some parents.

1 We call that now for convenience it's called
2 regressive subtype or regressive autism. Now, on that
3 slide it seems as if the development is normal up to
4 age 18 months, but recent studies which have looked at
5 this regressive subtype actually identify now that in
6 fact the development is not normal in the majority of
7 these children.

8 So Monsieur Rutter's work quoted that at
9 least half of the children who have the regressive
10 subtype actually are abnormal before the regression
11 occurs. There is a recent study by the nice work of
12 the CPAs in the U.S. and a large study looking at
13 regression versus nonregression where 70 percent of
14 children with a regressive subtype were actually
15 abnormal before their regression occurred.

16 Q Did you say 70, seven zero?

17 A Seventy-two percent, as I recall. So what
18 qualified is there are children who develop some
19 skills but then lose them, so they do lose skills, and
20 typically what they lose is language. They develop up
21 to five, 10, sometimes 20 words which are used for
22 some time, and then they don't use them anymore.
23 That's the way this loss of skills is usually
24 described.

25 Comparing it to the loss of language or

1 words, often social abnormalities become much more
2 obvious, but again when you look back to the
3 development before the loss although the loss is real
4 the development was not entirely normal in these
5 children in the majority of the cases.

6 Q And, Doctor, what percentage of children
7 with autism have the subtype of regressive autism?

8 A In current studies, the rate if you look at
9 children with autism or children with PDD-NOS, if one
10 takes, for instance, Kathy Locke's study, which is one
11 of the referenced studies, the rate is about 20
12 percent, so it's one child out of five.

13 It's true for autistic children and for
14 PDD-NOS as well that one child out of five would have
15 a setback in their development, some loss of skills
16 occurring usually in the fourth semester of life, but
17 with this loss always occurring before the age of two.

18 That's what distinguishes them from the next
19 profile I just brought up here in red you see on that
20 curve. That would be the developmental profile of
21 childhood disintegrative disorder.

22 Here it's very different. You have normal
23 development up to age two, two and a half, three, and
24 then a massive loss of skills and it goes way down,
25 and the end point is really severe. That's a very

1 different profile than the regressive subtype.

2 Q Doctor, staying with the issue of regressive
3 autism, in terms of language skills what do you look
4 for to determine if this is indeed a case of
5 regressive autism versus a case of I believe you
6 termed it fluctuating skills or plateaus type of
7 autism?

8 A Yes.

9 SPECIAL MASTER HASTINGS: And now we're on
10 Slide 16.

11 MS. RICCIARDELLA: Now we're on Slide 16.
12 Yes.

13 THE WITNESS: So in this Autism Diagnostic
14 Interview, which is the measure that we all use, there
15 are specific questions to evaluate regression in the
16 course of the development.

17 It is difficult to establish if a child
18 losses some skills. Suppose that the child is saying
19 mama, dada and maybe milk or duck one or twice. Can
20 we say that if he then becomes silent has he actually
21 lost language, or can we say that he was actually
22 using these words consistently?

23 It's hard to distinguish a true word from a
24 child who had just spoken a few times the word
25 occasionally and then stops pronouncing these words,

1 so in that particular instrument we try to establish a
2 baseline. We try to look at loss of words in a child
3 in which we can document that words were used
4 consistently with many for at least a period of time
5 so that we can really establish that there has been a
6 change in the development.

7 The particular criterion which is used here
8 is that we impose that to consider that there is a
9 loss of words or loss of language skills. We want the
10 child to have at least five different words, and we
11 don't count mama and dada because these are words
12 which sometimes they are just a sound approximation.
13 We want these five words to be used on a daily basis
14 for at least three months.

15 That's a way to establish a baseline of a
16 child who has at least some words which are used
17 meaningful for communicative purposes for a period of
18 time, so when it is used then you can really assess
19 there has been a change and a loss of skills.

20 This is to some extent arbitrary, but it
21 demonstrates the difficulty to evidence regression
22 based on retrospective accounts events, so you need to
23 sometimes differentiate a true loss from a child who
24 has just pronounced one word once and then you hear
25 one word once and then not again before two weeks and

1 then nothing.

2 That pattern is often seen, and it's
3 difficult to establish that there is a loss of these
4 words where it was just pronounced maybe once or twice
5 and not consistently and spontaneously with
6 communicative intent. So there is measurement
7 difficulty in establishing regression.

8 Q Doctor, are the first symptoms of autism
9 necessarily when the parents first recognize that
10 there is something going on with their child?

11 A I'm sorry, can you repeat?

12 Q Sure. Are the first symptoms of autism
13 necessarily when parents first recognize that
14 something irregular is going on?

15 A Yes.

16 Q I mean, can there be subtle signs of autism
17 that parents may not appreciate at the time that the
18 signs are actually occurring?

19 A You mean before the loss?

20 Q Before the parents recognize the loss, as in
21 something that clinicians can appreciate
22 retrospectively?

23 A Okay. Yes. Sure. Yes. Again, now
24 interviews, for instance, we have questions about the
25 age at which the parents start recognizing the

1 developmental abnormalities. So parents become
2 concerned at 18 months because the child is not
3 speaking, but then when we ask parents follow-up
4 questions, when we ask them, in hindsight, would you
5 say that your child was actually normal at age 12
6 months, and we have questions which are included in
7 this diagnostic interview, and many parents, in fact,
8 endorse that in fact they did not become concerned up
9 to the age of 18 months, but now that they know there
10 is a problem which is quite essential, and they look
11 back at what happened, they recall that someone said
12 he's too quiet, he's not babbling enough, or they look
13 at unusual behavior.

14 They didn't know what to make of it at the
15 time. So the hindsight question often gives a
16 perspective of onset which is, even if they think an
17 onset which is much earlier, that the time at which
18 parents became actually concerned in the course of the
19 development. And it's very important for us to
20 actually try to identify what is the phenotype of the
21 symptom pattern of the precursors of autism before
22 parents become concerned, because we are all aiming at
23 trying to diagnose autism at an earlier age, the
24 reason being that there is a lot of evidence now that
25 interventions, when they are applied early and

1 intensively enough, can actually make a difference,
2 educational interventions.

3 So there is a big effort at this point in
4 time to try to screen for autism at a very early age,
5 and when I say early age, it starts at the eighth
6 month of aging, a physician-based study in the UK in
7 1992, but now there are ongoing studies in Norway and
8 other cohorts of children where systematic screening
9 of infants which are typically developing in
10 population studies at 8 to 12 months or 14 months is
11 now made to try to detect autism very early. And
12 there is progress being made in that direction.

13 So it was important that we could identify
14 what are the early signs of autism in a child who is
15 at, say, 12 months of age.

16 Q Doctor, you and some other experts have said
17 that home videos reviewed retrospectively can be good
18 evidence of early signs of autism. Why is that?

19 A Yes.

20 Q This is now slide 17.

21 A Yes, and then there has been like two sets
22 of approaches to try to identify the early signs of
23 autism in infants, in fact. There is one which I will
24 not detail a lot, but which is ongoing in many, many
25 countries, which is really capitalizing on the fact

1 that because of the genetic basis of autism, we know
2 that when the child is diagnosed in a family, when
3 there is another child who is born, we know that there
4 is an increased likelihood that he will develop autism
5 or she will develop autism.

6 This risk is estimated at 5, 10 percent
7 depending on the author. That allows us to follow up
8 from birth onward young children we know are at risk
9 of developing autism, so that provides for efficient
10 study designs. And that is ongoing because that
11 fledgling (ph) study or interceding studies (ph), and
12 there is a baby network which is currently looking at
13 that.

14 And the first result of these studies show
15 that there are signs which identify social
16 difficulties which can be detected at 10 months of
17 age, 12 months of age, now in those studies. Not much
18 before. But before that was done, the first attempt
19 to identify these early developmental abnormalities
20 was made using a very creative approach, which was
21 also capitalizing on the fact that many families in
22 the 80s started to have cameras and they were filming
23 their children as they were developing.

24 So before, the investigator started to ask
25 families of children who were diagnosed with autism,

1 can you go back to your home films and see if you have
2 a scene of your child at an earlier point in time?
3 And if you ask different families different things,
4 there would be like different types of symptoms that
5 would be presented. So a way to standardize the
6 observations across families was to ask them, go for
7 their first birthday party because there are always
8 the ingredients here. People, it's social, there is a
9 cake, there is excitement, so you can really, across
10 birthday parties, there is the full ingredients can be
11 found, so you can actually rate children across
12 different families.

13 And the results were that we looked at
14 videos of children who are later diagnosed with
15 autism, but also children later diagnosed with mental
16 retardation or mental illness (ph), or typically
17 developing children. And these tapes were mixed up
18 and rated by experts who have autism expertise but
19 were blind to the particular group that the child
20 belonged to.

21 And this result which is summarized here, as
22 shown in different studies, it's obviously replicated
23 that early abnormalities can be found, and not all
24 abnormalities were found in each study, but across
25 studies, you can see the least of the difficulties

1 which can be found in these videos, and that is this:
2 abnormal eye gaze or abnormal eye contact; lack of
3 early communicative gestures like showing, like
4 pointing, as I said; deficits in joint attention which
5 is like pointing or following a point by their
6 parents; unusual posturing as well and abnormal motor
7 development has been described; lack of babbling or
8 poor, reduced babbling or unusual babbling sounds; the
9 lack of orientation to their name is a consistent
10 finding; also not looking at people has been in
11 several studies the single predictor which I think in
12 one study, 70 percent of later diagnosed children had,
13 they were not looking at people in their interactions,
14 and that single behavior had to classify correctly a
15 number of these children.

16 So you can see there the other signs. And
17 the last point is that in several of the studies,
18 people have looked at the interactive style developed
19 by the parents, and it's also shown in our clinical
20 settings, that in these children, although the
21 abnormalities are fertile (ph) and the parents do not
22 maybe realize them, and what they do is they try to
23 develop interactive styles which compensate for the
24 lack of response of the child.

25 So that, for instance, the child is not

1 giving enough eye contact. It's hard to get his
2 attention. So what parents would do typically would
3 be they would move their body or their face in the
4 visual field of the child to capture his attention.
5 It is a very subtle adjustment that you do, and you
6 don't realize it. Parents, they do it all the time.

7 Or in order to get the attention of the
8 child, if the child doesn't respond to his name, they
9 would repeat that or they would use a high-pitched
10 voice or they would use different things which have
11 worked to attract the attention of their child. And
12 you can see this compensatory strategy by caregivers,
13 which often gives excessive prompting or repeated
14 prompting or cuing of their child to get the
15 interaction going on.

16 Q Doctor, what does the autism research
17 community know about the rate of autistic spectrum
18 disorders among social classes?

19 SPECIAL MASTER HASTINGS: Now we're at slide
20 18.

21 MS. RICCIARDELLA: 18, sir.

22 THE WITNESS: The current view is that
23 autism occurs in all social patterns. There is no
24 association with social classes.

25 BY MS. RICCIARDELLA:

1 Q And according to your slide, there's no
2 difference among geographical locations. Is that also
3 correct?

4 A Yes. As far as what is established now, the
5 incidence of autism appears to be comparable across
6 different areas or countries. It has been described
7 in most countries. Although there might be some
8 differences in rates which are published, there is no
9 strong evidence there would be a difference in
10 incidence across different countries.

11 Q And your slide says that there is a male-
12 female ratio of 4 to 1 for autism.

13 A The next two slides, this one and the next
14 one, are the two most well-backed (ph) findings which
15 have been described in autism research for decades,
16 which are still requiring an explanation. The first
17 one is that there is an excess of male in this group
18 of conditions. The four males for one female ratio
19 that you see here is an average. So it's an average
20 of many samples that would be typical of an autistic
21 sample.

22 Now, there is variation of this ratio
23 according to the level of development. So, if one
24 looks at children with autism or PDDs who have no
25 mental retardation who are high functioning, then the

1 male-female actually becomes higher. You have like
2 six or eight boys for one girl affected in the high-
3 functioning samples.

4 And by contrast, if you go into the children
5 who have mental retardation, moderate to severe, then
6 the gender ratio goes down. There is always a
7 preponderance of males, but it's like 1.7 males for
8 one girl, or two boys for one girl. So what it means
9 is that, to summarize that, girls tend to be less
10 often afflicted with autism, but when they are
11 afflicted, they tend to be more severely affected on
12 the lower developmental layer of range.

13 Q And you mentioned retardation. If I'm
14 understanding your slide correctly, 70 percent of
15 people with autistic disorder also have mental
16 retardation of some form?

17 A Yes. Mental retardation is a correlate of
18 autism which is significant. This figure is for
19 autistic disorder. For PDD and the rest, it's not
20 very well known, probably less than that. But for
21 autistic disorder, it's about 70 percent. Studies
22 vary from 60, 50 percent in recent studies, but up to
23 75 or 80 percent. On average, they say two children
24 out of three with an autistic disorder diagnosis score
25 on standardized tests of intelligence in the mental

1 retardation range, which means IQ under 70.

2 Q And your last point of your slide says the
3 incidence of epilepsy is 20 to 30 percent of
4 autistics, is that correct?

5 A Yes. This is a well-established finding,
6 again, which is unique to the autistic population.
7 This figure actually, it's a lifetime rate. It means
8 that if you follow up children from their diagnosis up
9 to adult life, 20 or 30 percent of them would develop
10 at one point in their lifetime seizures or epilepsy.

11 What is unique in autism is that, unlike
12 mental retardation, mentally retarded children who
13 don't have autism have often seizures or epilepsy, but
14 they often develop the first epileptic fits or
15 seizures early in their life, in the first three,
16 four, five years of life. In autism, there is a group
17 which is like that, with early onset, but the majority
18 seems to develop epilepsy during adolescent years, and
19 this is quite unique, and has been known for 30, 40
20 years.

21 We don't understand why it is the case with
22 them that there is a peak of incidence in the
23 adolescent years, but it's well-established. And it's
24 not found in other kinds of populations.

25 Q Are seizures more common in the regressive

1 sub-type of autism?

2 A No, it's actually been tested by large
3 studies done by Isabelle Ruppert, which is a child
4 neurologist in New York, and Roberto Tuchman, who have
5 actually looked very specifically at this question, is
6 regressive autism associated with epilepsy, and they
7 did not report an association with epilepsy.

8 Q Doctor, are there any known causes of
9 autistic spectrum disorder? And I know now you want
10 to refer to slide 19?

11 A Yes. When we do assessments, we look for
12 these children have been evaluated with a range of
13 medical investigations, which include like blood
14 tests, looking at metabolic disorders and genetic
15 disorders which would be correlates of their autism.
16 Again, autism is different as a behavioral disorder,
17 so that's one thing, and then we look at whether or
18 not in addition to their autism there is a medical
19 condition which could be associated, either co-
20 occurring or associated statistically with autism.

21 And of the list of medical disorders which
22 is well-established to be leading to an increase in
23 the risk in autism, you can see that there are a
24 number of medical conditions, and they turn out in
25 this slide to be all genetic disorders. The two most

1 important on this list are tuberous sclerosis and
2 Fragile X.

3 Tuberous sclerosis is 100 times more
4 frequent in autism compared to the general population,
5 although it does not account for many cases of autism.
6 So the rate of TS in autism is no more than 1
7 percent, but it's still 100 times more than the rate
8 in the general population.

9 And Fragile X is a disorder where there is a
10 gene on the X chromosome which is methylated and
11 linked to the absence of the position of a protein.
12 It's called, it's the most common cause of inherited
13 mental retardation in human populations, and about 30
14 to 40 percent of children who have Fragile X meet
15 criteria for autism. If you look the other way
16 around, it's around 3 percent, 4 percent of children
17 with autism who do have Fragile X.

18 So if you cumulate all the possible medical
19 causes which might explain the autism in a child, you
20 have up to 10 percent on average of cases of autism
21 which can be explained in terms of being attributed or
22 ascribed to a medical disorder, often one of these
23 which have a genetic basis, which means that in the
24 rest of these autistic populations, that 90 percent of
25 them, even when you do very complex medical work-ups,

1 you don't find any kind of medical conditions that you
2 can put your finger on.

3 And a legacy in science, we use the term
4 'idiopathic cases,' meaning that there is no
5 recognizable cause. It means that we don't know where
6 it comes from.

7 Q Are there currently any studies looking into
8 possible other etiologic causes of autism?

9 A Yes. There have been a lot of studies
10 looking at, for instance, psychosocial interferences
11 are of no role in the etiology of autism. There was a
12 phase where parenting styles or parental interactions
13 were incriminated as being a cause. Of course, there
14 is nothing to that. Autism does not arise because of
15 poor parenting or poor rearing circumstances.

16 A range of other causes have been looked at.
17 For instance, infections, infectious disease has been
18 evaluated, and by and large, there is no strong
19 association with any of the infectious diseases. Flu
20 has been looked at. Measles have been looked at, and
21 other kinds of infections have been, and there is no
22 positive associations.

23 People have looked at patterns of seasonal
24 birth, because often infections have a seasonal
25 pattern, and so if there was an association, you

1 should see a seasonal pattern in the birth. All
2 studies have been showing nothing basically.
3 Obstetric complications have been looked at as well,
4 and they do not appear to be an etiology of autism.
5 So that's why the rest is idiopathic, so we don't
6 know.

7 Q Doctor, what does the autism research
8 community know about the genetics of autism?

9 A Yes, I would say just briefly something.
10 The genetics of autism started in the '70s, so in
11 1977, the first twin study was published in England,
12 and then there was a follow-up later by Bailey, and
13 you see the study by Bailey here.

14 Q For the record, you are referring to slide
15 20, correct?

16 A Yes. Now, this is a large twin study that
17 got published in 1995. It's a UK-based study of same-
18 sex twin pairs, and the critical finding, there are
19 two critical findings of that study. The yellow bars
20 are the concordant traits in twin pairs. So if you
21 look at the MZs, which are monozygotic twins, which
22 are one hundred percent genetically alike, when one
23 twin has autism, there is a 70 percent likelihood that
24 the co-twin will be affected as well.

25 Whereas, if you look at dizygotic pairs,

1 which are like fraternal twins who share only 50
2 percent of their genes, in that study, when one was
3 affected with autism, in fact there was no other co-
4 twins who would have the disorder. So what matters
5 here is the difference between concordance rates
6 between dizygotic twins who share only 50 percent of
7 their genes on average, and the concordance which is
8 much higher in monozygotic twins, which is about 70
9 percent.

10 We can discuss or argue what is the exact
11 concordance rate, but it has been replicated in
12 different studies. It's high, 70, 80, 90 percent in
13 different studies. And that shows the discrepancy in
14 concordance rates is a direct measure of the
15 contribution of genetic factors in autism.

16 And the second finding of that study is that
17 if you will look at the other bar, there is the red,
18 the green, the purple. These were to look not at
19 autism in the co-twins, but look at developmental
20 abnormalities which involve often language
21 development, social development and other types of
22 behaviors. When they looked at the co-twins who
23 didn't have autism, they found that a number of them
24 had developmental abnormalities in these domains which
25 were conceptually the same domains that we see

1 affected in autism but much lesser in terms of
2 severity.

3 So they were not deriving a diagnosis of
4 autistic disorder or PDDs in these co-twins, but
5 clearly the developmental difficulties were like what
6 you see in autism but much less in severity. And that
7 led to the idea that what is transmitted in families
8 is autism but also a genetic propensity to a set of
9 broader developmental abnormalities, and we call that
10 now the broader autism phenotypes.

11 It's important to know because there is
12 research informative for our discussion which refer to
13 the BAP or the broader autism phenotype. So the
14 broader autism phenotype is what is seen in siblings
15 or relatives of autistic children (ph), and we believe
16 that these subjects in these families probably do
17 have, carry some of the genes involved, although not
18 the full complement. I'll leave Dr. Cook to speak
19 further on that issue.

20 Q Now, Doctor, in your report, you mention
21 that ASDs cluster in families. What do you mean by
22 that?

23 A Yes, so the twin studies really established
24 that there was a strong genetic influence in autism,
25 and that was then repeated in multiple family studies

1 where we have looked, we have calculated the incidence
2 of autism or PDD in siblings following a child already
3 diagnosed in a family. So if we look, this is a
4 summary of the rates that we have.

5 SPECIAL MASTER HASTINGS: Now we are on
6 slide 22 -- 21, correct? 21. Go ahead.

7 THE WITNESS: So one can start with a
8 general population rate for autism, which is 20 per
9 10,000 based on recent figures, and then a
10 conservative estimate for the risk in siblings, which
11 is the same for dizygotic twins, is about 5 percent.
12 That shows that when you are a sibling of a child, an
13 individual with autism, you have 25 times the risk
14 compared to the general population. So the risk is
15 raised 25-fold if you are a sibling, DZ twin, of an
16 individual with autism.

17 And if you look at MZ twins, again taking
18 conservative estimates, the risk is 300 times higher
19 than the risk of the general population. That really
20 shows, these relative rates show that the risk of
21 autism is increased as a function of your genetic
22 similarity to an individual who has the condition.

23 BY MS. RICCIARDELLA:

24 Q Doctor, in your report, you briefly touched
25 on what the autism research community knows about the

1 neuropathology of autism, and I know you have three
2 slides that are illustrative of what they're doing.

3 A Yes. Yes.

4 Q Would you walk us through those three
5 slides? I think the first slide is obvious. Slide
6 22, that's a picture of a brain, correct?

7 A Yes. It's a picture of a brain which is a
8 picture of an autistic brain. It's just to summarize
9 that the brain has been looked at in neuropathology
10 studies which are difficult to conduct, how to get the
11 brain, but they have been done since the 70s, and more
12 recently there is an acceleration of this research.

13 This slide is just to indicate, this is a
14 picture, it looks like a normal brain. So when we
15 look externally at the brain of an autistic
16 individual, there is no obvious abnormality. There is
17 no part which is missing. There is nothing which is
18 abnormal in terms of the macroscopic structure of the
19 brain. So that's a consistent finding.

20 The next slide, this is a slide of the
21 cerebellum, and across different studies which are
22 done by different investigators, one of the most
23 consistent findings has been to document that in the
24 cerebellum, there is a class of cells which are called
25 Purkinje cells, which are important to the function of

1 the cerebellum, which seem to be lost or decreased.

2 And you can see on the right-hand side, the
3 lower slide which you see, this is the cerebellum
4 cortex of a control, and you can see there is a high
5 density of Purkinje cells. On the left side, the B
6 slide, you can see that the density of the cell is
7 much less, that it is pale, and that indicates a loss
8 of these cells, Purkinje cells. A very wide
9 documented finding.

10 SPECIAL MASTER HASTINGS: Now, what kind of
11 cells were we talking about in the cerebellum?

12 THE WITNESS: Purkinje is P-U-R-K-I-N-J-E,
13 Purkinje cells.

14 SPECIAL MASTER HASTINGS: Thank you.

15 THE WITNESS: So the next slide?

16 BY MS. RICCIARDELLA:

17 Q The next slide is slide 24?

18 A Yes, and the importance of these findings is
19 it is printed on that slide, which is slide 24, you
20 can see a Purkinje cell which is on the top, and what
21 is important is that the fiber, the axon which is
22 denoted by 'C,' which comes to be in contact with this
23 Purkinje cell, in the development, what happens is
24 that the cerebellum cell, the Purkinje cells, receive
25 connections from neurons which are located in the

1 brain stem, more particularly, in the structure which
2 is called the inferior olive.

3 And these neurons send axons which are
4 called climbing fiber axons, which then connect with
5 these Purkinje cells at one point early in the
6 development of the brain. And in fact, we know that
7 this connection is established, at most, at 30 weeks
8 of gestation. When these two cells connect, they are
9 sort of glued together and they just function together
10 as a tandem.

11 And if subsequently, the Purkinje cell is
12 destroyed for any reason, what happens is the Purkinje
13 cell disappears, but also, there is a loss which is
14 called retrograde cell loss, which affects the
15 climbing fiber axons from the inferior olive. So it's
16 important to know because in the neuropathological
17 studies, the Purkinje cells were absent in theses
18 brains, but then the neurons, the climbing fiber
19 neurons, were present.

20 They were there. And that indicated, and
21 this is the work of Bauman and Kemper, the authors the
22 work (ph), that indicate that the loss of Purkinje
23 cells must have happened before the 30th week of
24 gestation. Otherwise, if they had been connected at
25 that time and the loss of Purkinje cells had happened

1 after the 30 weeks of gestation, there should be a
2 loss of the climbing fiber axons, okay?

3 And this is known in neonate pathology or
4 at-birth pathology, any loss of Purkinje cells later
5 in life leads to the retrograde cell loss of these
6 particular climbing axons. And it's not what we find
7 in autism. In autism, they are there. It is there,
8 present, indicating that there has been no connection
9 in the course of the brain development in the first 30
10 weeks of gestation between these axons and the
11 Purkinje cells.

12 So that shows us that there is an early
13 abnormal development before gestation in autism.

14 SPECIAL MASTER HASTINGS: All right. Why
15 don't we take our morning break at this point? So
16 let's take a fifteen-minute break. I've got 10 after.
17 We'll convene at 25 after 11.

18 (Whereupon, a short recess was taken.)

19 SPECIAL MASTER HASTINGS: All right. We're
20 going to go back on the record here, and Dr. Fombonne
21 is still on the witness stand, and Ms. Ricciardella,
22 please go ahead.

23 MS. RICCIARDELLA: Thank you, Special
24 Master.

25 BY MS. RICCIARDELLA:

1 Q Doctor, are there objective signs of
2 abnormal brain development in some autistic children
3 that can be observed clinically?

4 A Yes.

5 Q What are those signs?

6 A One of them is what is called macrocephaly,
7 which is an enlarged head circumference, and this was
8 actually described by Tanner in 1943. With a series
9 of eleven cases, he measured the head circumference,
10 and without any attention to that, he actually
11 documented that five children out of the 11 had a
12 large head, and that went unnoticed for 30 years, and
13 it resurfaced in a twin study done in the UK where
14 they noticed again that the twins in their studies had
15 large heads.

16 Following that observation, several
17 systematic studies have looked at this question, and
18 you can see on that particular slide, 25 ---

19 Q Slide 25.

20 A -- that this, combined with some later
21 analysis, that the rate of macrocephaly in autistic
22 sample is about 20 percent. Macrocephaly is a
23 clinical sign because it's -- if we keep (ph)
24 measuring the head circumference with a tape measure,
25 and we have knowns of head circumference from birth to

1 age 18, and therefore we can plot any measurement of
2 any single individual against these knowns and see,
3 compare the observed head circumference in a child to
4 the distribution of head circumference in the
5 population.

6 Macrocephaly is defined as a statistical
7 deviance from the mean, and it means that the head is
8 over the 97 percentile, meaning that in the general
9 population, you would expect that, in a random sample,
10 that 3 percent of people would have a large head
11 defined as being over the 97 percentile. In autism,
12 this proportion, instead of being 3 percent, what we
13 would expect, is about 20 percent.

14 So that was the first indication that there
15 was abnormal brain growth in autism, and what is
16 important to know is that in young children, infants,
17 toddlers, there is a strong correlation between head
18 circumference and brain size, so head circumference at
19 that age is a very good measure of brain size. In all
20 the individuals there is a correlation at any age, but
21 in young children it's a very high correlation.

22 So can I have the next --

23 Q Next slide, slide 26.

24 A Slide 26 concerns this observation. This is
25 a series, I think, of 12 brains which have been

1 studied by Bauman and Kemper, and with them, they
2 measured the brain weight and then they compared that
3 to expected brain weights based on various studies,
4 and you can see that the difference on the right-hand
5 column suggests that in a number of cases, the brain
6 exceeds, by a large amounts sometimes, the weight that
7 you would predict it should have.

8 So it means that this large head is
9 associated with a brain which is actually heavier.
10 And this finding here (ph) has also been concerned
11 with MRI studies. If we could have the next slide,
12 which is slide 27, and on that slide you can see that
13 the head circumference and the head volumes of
14 children in the Dawson study have been measured, and
15 what is important here is that, at birth, it seems
16 that the head circumference is normal.

17 There is no evidence that the brain is
18 increased in size at birth, but as you see on the left
19 picture, around 3 or 5 months of age, there seems to
20 be an acceleration of brain growth, and then the brain
21 becomes larger and between 6 and 14 months of age, it
22 deviates from the normal, the average, to a
23 significant extent.

24 So this pattern of brain growth seems to
25 apply or start to develop sometime within the first

1 year of life in the second semester, or in the second
2 trimester or second semester of life, and there is an
3 acceleration of brain growth, brain size and head
4 circumference which seems then to abate a bit. So at
5 age 2, 3, 4, this acceleration starts to decrease.

6 In fact, there was a study published by
7 Dawson this year, I think, 2007, where they looked
8 again very carefully in a sample of about 30 children
9 with autism at this pattern of head growth in the
10 first three years of life, and they redocumented very
11 well that there is a steep acceleration of head size
12 during the first year of life, and it then plateaus in
13 the second year of life, and at a time where the
14 behavioral symptoms start to emerge.

15 So there is this pattern of accelerated head
16 growth in the first year of life, and then it seems to
17 plateau in terms of the speed of the acceleration of
18 head growth decrease in the second year of life. So
19 that's one of the most well-backed (ph) findings in
20 the recent years. It is not very clear what is
21 happening in the brain.

22 There have been various MRI studies which
23 indicate that there is an enlarged white matter
24 volumes in the cerebellum and also in the total brain,
25 but studies are not entirely consistent with the areas

1 of the brain which would be subject to these increased
2 volumes, except that it seems that frontal lobe seems
3 to be -- frontal cortex seems to be preserved.

4 Q Doctor, does the autism research community
5 now consider autism to be a disorder more likely than
6 not as a prenatal onset?

7 A Yes, a high number of scholars would agree
8 with that statement. It's really combining the
9 evidence from different sources of information. As I
10 mentioned before, if we look at neuropathology
11 findings, the findings which are the most consistent
12 are the loss of Purkinje cells and, as explained
13 before, this must happen during the gestation, at an
14 early stage of brain formation, because of the
15 preservation of all the variant neurons.

16 In terms of etiologic research, there have
17 been a few environmental exposures which have been
18 documented to increase the risk of autism or autistic
19 syndromes, and all of these exposures, as you can see
20 on the second block on this slide, refer to exposure
21 which occur during pregnancy. So for instance, there
22 is one infection which is called rubella. When it
23 occurs during the gestation, it can lead to
24 devastating effects in the child.

25 There was an epidemic of congenital rubella

1 in the US in 1963, '64. Children who were affected
2 were followed up, examined, and a high number of them
3 autistic syndromes, were slightly different than
4 classical autism, but they had autistic features.
5 Now, it's a historical cause of autism because
6 nowadays, there is no more congenital rubella, unless
7 in some countries, but it's very rare.

8 Then there have been a few other studies
9 which have looked at exposure during the gestation to
10 particular substances, and the thalidomide exposure is
11 an interesting case. People will remember that this
12 medication was used against nausea during pregnancy at
13 the time, and it was discovered that a lot of kids
14 born from mothers who had taken this medication during
15 pregnancy were born with limb malformations, in
16 particular, and it was discontinued immediately.

17 Children born from these cohorts of mothers
18 exposed to this medication were subsequently followed
19 up, and in some of them, in fact, some of them
20 developed autism and the number of them who developed
21 autism was too high to be just a co-occurring
22 phenomenon. And those children who were exposed to
23 thalidomide and had autism also didn't have limb
24 malformations. They had ear malformations but not
25 limb malformation, and that suggests that they were

1 exposed during a particular window of time which has
2 to be before day 24 in the gestation. It has to be
3 between day 20 and 23 due to what we know about
4 embryonic development.

5 So that correlates with an opportunity to
6 look at particular time exposures which might be
7 increasing the risk of autism, and the same for the
8 other medications. The point is not to say that many
9 cases of autism are explainable in terms of these
10 exposures, but these exposures are useful in providing
11 models of exposure to particular substances which are
12 toxic for brain development, and they create models
13 for us to understand what's going wrong in brain
14 development, but they all point to an early exposure
15 during gestation.

16 There is a third type of finding which is
17 coming from dysmorphology studies. The best study
18 probably to research for that aspect is the study by
19 Miles which is based on a large sample of I think
20 about 150 children with autism, consequently referred
21 to facility, I think it's in Missouri, where they had
22 particular expertise in dysmorphology, so they
23 consistently examined the children diagnosed and
24 looked at dysmorphic features.

25 They have different ways to do that, and

1 they looked at children who had three or more
2 dysmorphic features, which is a relatively high
3 threshold, and showed that 20 percent of children
4 consequently referred with an autism spectrum
5 diagnosis had actually dysmorphic signs, an again,
6 dysmorphic signs would usually involve facial
7 features, clearly indicating that something is going
8 wrong in brain development during embryo genesis.

9 Then finally, there is a study which was
10 done in California using archived cord blood spots in
11 children who were then subsequently diagnosed with
12 either autism or mental retardation or cerebral palsy,
13 and there was a group of controls. And they looked so
14 they could measure just at birth in these blood spots
15 a certain number of peptides which include the
16 intestinal peptides, the brain-derived neurotrophic
17 factors, and a few other peptides which are all
18 involved in neurotrophic function and that helped in
19 the neuronal development and connection when the brain
20 is forming.

21 And at birth, what they found is at birth,
22 children with autism and children with mental
23 retardation had abnormal levels of several of these
24 peptides. Other peptides were not different from
25 controls, but these were different compared to

1 children who are either normal or had cerebral palsy,
2 which were no different than normal. So those
3 children with mental retardation and autism had
4 abnormal findings in that study, which clearly can
5 only be explained in terms of something happening
6 during the pregnancy.

7 And interestingly enough, in that study, if
8 one looks at a breakdown of the routine samples by
9 regression status, there was actually I think 21
10 percent of this sample of autistic children who had a
11 regressive pattern, and they were as abnormal as the
12 nonregressive autistic children, meaning that even
13 though they had a regressive pattern later in life,
14 the biochemistry findings were as atypical as the
15 nonregressive autistic children.

16 Q Doctor, finally, have any treatments for
17 autism been known to be successful?

18 A Yes. Autism has no cure, and where there is
19 no cure, there are thousands of treatments, and you
20 can see on that slide, it's a long list which could be
21 expanded --

22 Q Slide 29?

23 A Slide 29, that treatment which do not work.
24 They do not work, but they are nevertheless often
25 used. Two of them maybe merit particular attention.

1 The one is facilitated communication, which is a kind
2 of psycho-social intervention which was proposed at
3 one point and followed by multiple groups in the world
4 in terms of trying to develop communication strategies
5 using computers and communication aides with children.
6 It was then researched very carefully by different
7 researchers, and the more they used rigorous control
8 design, the more it appeared that there was no
9 efficacy of this intervention.

10 Another one which is more in the biomedical
11 field, which is the secretin infusion, again, had an
12 interesting history in the sense that case studies of
13 two or three children with autism who were going
14 through GI explorations who were infused with
15 secretin, which is used in medicine to explore
16 pancreatic and gastric functioning, were claimed,
17 based on an open, uncontrolled study to be suddenly
18 improved.

19 And following this initial report which was
20 uncontrolled, there was massive excitement worldwide
21 about using secretin, and multiple groups in the world
22 advocated secretin, they had to do it, up to the point
23 that NIH decided to, because they were confronted with
24 problems in supplying secretin everywhere, decided to
25 support the conduct of three independent randomized

1 clinical trials, which were conducted years later
2 because it takes time, and all of these trials showed
3 that there was absolutely no efficacy. So that caused
4 some parents and professionals to shy away from this
5 intermission we have no basis, and no plausibility and
6 no efficacy to discontinue that, although there are
7 still some people who do believe in it supposedly.

8 So the point I want to make here is that
9 I've been in the field of autism, including theories
10 and treatments which were once proposed by
11 psychiatrists like the refrigerator mother theory and
12 the bitter then furies. There have been a flurry of
13 other motives of autism or treatments of autism which
14 have been like fashionable at the time but not founded
15 on strong evidence.

16 The evidence today suggests that we have
17 interventions that work. They're all based on
18 educational techniques or behavioral interventions
19 which need to be intensive enough, applied early as
20 possible and we then subsequent can make really
21 substantial developmental gains, although a cure is
22 not yet at stake. Occasionally drug treatment can
23 help but not on the core features of autism, mostly to
24 manage behavioral problems which they sometimes have
25 in addition to the autism.

1 Q Doctor, turning to the facts of this case,
2 the case of Michelle Cedillo, have you reviewed the
3 medical records of Michelle Cedillo?

4 A Yes, I did.

5 Q And do you agree with the diagnosis of
6 autism in this case?

7 A Yes. I think there is no doubt that she is
8 meeting criteria for autistic disorder. It's based on
9 my review of all professional reports which conclude
10 that. Also, I reviewed particular reports which were
11 providing detailed behavioral descriptions of Michelle
12 which were quite consistent with this diagnosis.

13 SPECIAL MASTER HASTINGS: And now we're on
14 Slide No. 30. Go ahead.

15 MS. RICCIARDELLA: Thirty. Correct. Okay.

16 THE WITNESS: Then the diagnosis is clearly
17 autistic disorder, and the history of Michelle is
18 typical in terms of the developmental course that she
19 followed. Parental recognition, which one parent
20 became concerned. What happened in terms of their
21 first concern and then the slide that she was
22 diagnosed a year or 15 months later, which is quite a
23 typical story, and the fact also that she has mental
24 retardation, which is an associated feature which is
25 important in terms of understanding her behavior and

1 for her management, and also, that she has epilepsy as
2 was indicated before.

3 It's on the previous slide. So, yes. The
4 epilepsy for instance in Michelle was an onset at age
5 10 is quite consistent with what we know about the
6 association between epilepsy and autism. Even though
7 it might have been triggered or precipitated by some
8 medication, she had probably vulnerability to epilepsy
9 associated with her autism.

10 BY MS. RICCIARDELLA:

11 Q Doctor, so Michelle is also mentally
12 retarded. Is that correct?

13 A Yes. Yes. Under the multiple testing which
14 has been done she's most evidence going in the range
15 of severe mental retardation.

16 Q Is there anything unique or different about
17 Michelle's autism that what you encounter in your own
18 practice?

19 A No. As I said she looks like in terms of
20 her developmental history and the symptom pattern like
21 many children I have seen who have severe autism
22 associated with retardation. As I said, the first
23 behavioral concerns were noted in fact in the medical
24 records on March 15 when parents reported that she had
25 stopped talking, and I think based on several

1 documents similarities, the recognition by parents
2 that something was somewhat wrong, you know?

3 They would have known, okay, at some time
4 between January and March 1996 date abnormalities that
5 the mother gave on several occasions, and also on
6 professional reports like a speech therapist report in
7 1997, Dr. Roth's report in 1997, or the private
8 accounts of a gradual onset during that time period.

9 Q Now, Doctor, you talked earlier about the
10 signs of autism that may not be apparent to
11 parentalize at the time they're occurring. You
12 reviewed Michelle's medical records. Did you see
13 anything that might suggest Michelle was not
14 developing entirely normally prior to her MMR
15 vaccination?

16 A Yes, and again, critical to the object of
17 this trial is the argument that she developed normally
18 up to the point when she had MMR, so I focused in my
19 review of her medical records and of the videos on
20 this question. Based on my review of all sorts of
21 documentation which was available to me there is clear
22 evidence that she was abnormal before the MMR
23 vaccination, and that comes from four different lines
24 of evidence.

25 SPECIAL MASTER HASTINGS: Now you're looking

1 at Slide 32, Doctor. Is that correct?

2 THE WITNESS: Yes. Slide 32.

3 SPECIAL MASTER HASTINGS: Go ahead.

4 THE WITNESS: The first evidence is that she
5 showed early onset social and communicative
6 abnormalities. There is also strong evidence of motor
7 delay which is substantial in her development. There
8 is certainly evidence that she had abnormal brain
9 growth in the very early stage in her development as
10 indexed by the macrocephaly. Then there is evidence
11 from the observations of the videos, which I will
12 provide later.

13 BY MS. RICCIARDELLA:

14 Q Let's take those one at a time. What
15 evidence did you find of early social communicative
16 abnormalities?

17 A Well, there are several accounts I should
18 say in the professional reports. That as a baby she
19 was very content, very quiet, not demanding. These
20 have been like qualities in an infant which are often
21 retrospectively attached to children who later are
22 diagnosed with autism. That's one aspect.

23 In terms of her social development, she was
24 in a sense late in terms of social smiling. So it is
25 reported in Dr. Roth's report I think that she didn't

1 smile before four to six months of age. This is very
2 late. Children smile much earlier than that, so she
3 was late in that social development aspect. Then I
4 think more importantly it's very clear that her
5 language was delayed. Even if we assume that by
6 December 19 or 20 she had up to 10 words, which would
7 be at most what she had, actually the examples are
8 lacking in terms of which words she was actually
9 using.

10 We don't know if they were using
11 consistently with meaning, probably not I would say,
12 but Dr. Roth reports that in fact she used up to 10
13 mostly in imitation suggesting that Michelle was
14 repeating words occasionally that she heard, but she
15 was not really talking or using these words
16 consistently with meaning and spontaneously.

17 So even if we accept that she had like 10
18 words it's important to refer to what we know about
19 normal development at that age. Here, I present on
20 that Slide 33, these are population norms about
21 vocabulary production at that age.

22 It is based on an instrument which is called
23 the MacArthur Communicative Development Inventory,
24 which is a widely used scale to assess language and
25 communication development starting with infants from

1 age eight months to 16 months, and there is a toddler
2 form as well which follows. This instrument is a
3 parents' report.

4 So it's a scale that you can give to
5 parents, and there are multiple questions about what
6 the child does understand, what kind of gestures the
7 child is using and there is a survey of 396 words I
8 think that parents are asked to look at and they must
9 say if the child understands that word or if he
10 understands and uses that words, so you can score that
11 in different ways.

12 This instrument, which is again based on
13 parental reports, so that's why I chose it in turn
14 because we can then compare what the norms show to the
15 evidence given in the medical record based on maternal
16 reports as being norm for the population of infants
17 and toddlers in the U.S. There is a normative sample
18 which was studied with young children and their
19 parents, and selected in Seattle, San Diego and New
20 Haven as I recall, that allowed them to produce these
21 norms.

22 You can see on this slide the thicker line
23 indicates the fiftieth percentile. If you look at 16
24 months of age, which is basically the age that
25 Michelle had, she had 15 months of age and three-

1 quarters at the time of MMR, so she would have been
2 expected to have about 40 words in vocabulary if she
3 was average.

4 In fact, this slide is combining the two
5 genders, girls and boys, and if we are looking at the
6 girls specific norm she should actually be having more
7 words because girls are a bit ahead of the game
8 compared to boys, but it's not important to the
9 argument. If you look at that even with 10 words she
10 will be falling in the bottom of the distribution for
11 her age.

12 If we look at the words that were reported
13 she would score like two or three words on this CDI
14 inventory, therefore falling largely under the fifth
15 and maybe even a lower percent than that. So it's
16 clear just based on that even if assume that the 10
17 words were used that she was delayed in her language
18 development based on this particular instrument, which
19 is known and is referenced for the population of U.S.
20 children. So we cannot say that at 15 months and a
21 half she had normal language. She was delayed in her
22 language development.

23 Q Doctor, I think your second category you
24 said was evidence of motor delay. What evidence of
25 motor delay do you have, and would you like to

1 illustrate that through a video?

2 A Yes, but before we look at the video there
3 is a clear account in the medical records that she
4 didn't meet major developmental milestones. So for
5 instance she was not sitting independently before 11
6 months of age. She started to crawl only at nine
7 months of age. The walking is more difficult to
8 establish, but in some areas of the record it said 15
9 months, 16 months.

10 In fact, I reviewed among the videos one
11 which is at 17 month and a half where she should be
12 walking and as we will see she is not walking
13 independently yet. So can we maybe see the video?

14 MS. RICCIARDELLA: Can we stop it? Because
15 there's no video.

16 SPECIAL MASTER HASTINGS: For those at home
17 we're going to be watching a video here.

18 (Video played.)

19 THE WITNESS: It's a small clip, but if you
20 follow, you can review it again, you can see that she
21 doesn't walk independently and she is somewhat
22 unstable in her posture. If you follow the whole
23 scene it's the same. She never walks independently.
24 When she stands up she has to put her hands on some
25 kind of toy or something. So she doesn't have

1 independent walking at that age.

2 This is one example, but again, if you look
3 at the development she failed to meet not all
4 developmental milestones consistently since she was an
5 infant. Again, sitting independently at 11 months of
6 age is much delayed.

7 SPECIAL MASTER HASTINGS: Doctor, just to
8 clarify for the record here you just showed a few
9 seconds of a video that was taken at a playground it
10 looked like, and that was at February 6, 1996. Is
11 that correct?

12 THE WITNESS: Yes, I think so. Yes.

13 SPECIAL MASTER HASTINGS: Slide 34 gives
14 that date.

15 THE WITNESS: Yes.

16 SPECIAL MASTER HASTINGS: And you're saying
17 your analysis of that, you looked at the whole video.
18 There was more footage of that day at the playground
19 than you showed now, but you're saying you looked at
20 the entire thing. In what I saw there she was walking
21 but with someone holding her hand.

22 THE WITNESS: Yes.

23 SPECIAL MASTER HASTINGS: And you're saying
24 during the whole video she walked only with someone
25 holding her hand.

1 THE WITNESS: Yes, and you can see that's
2 she's actually tripping at one point, and she doesn't
3 keep her balance, so she has to be held. At one
4 point we see her standing alone, but she has to use a
5 kind of support system to stand alone. So at that
6 age, which is quite old for walking, she still doesn't
7 have independent walking on that particular clip, and
8 if you extend the clip, the same description.

9 If you look at other videos which precede
10 there is no point there is evidence that she walks
11 before that. There is one scene I think where just
12 after the MMR or just before she's pushing a little
13 carriage, but again, it's a helper to walk. She
14 doesn't walk independently. She is delayed in terms
15 of her walking, and it's not because of the MMR
16 because she was delayed in terms of motor methods much
17 before.

18 Sitting independently at 11 months of age is
19 a very delayed milestone so to speak. Young children
20 sit usually at six months of age, okay, and eight
21 months is really a cut off for being delayed for this
22 particular motor milestone, so she was delayed across
23 the board in terms of her motor milestones. As you
24 will see there will be other evidence that you can see
25 about posture instability and difficulties in terms of

1 motor development at a later stage.

2 SPECIAL MASTER HASTINGS: All right. Go
3 ahead, Ms. Ricciardella.

4 BY MS. RICCIARDELLA:

5 Q Doctor, I believe your third category was
6 you noticed early abnormal brain growth as indexed by
7 macrocephaly. Can you describe what evidence you saw
8 of that in Michelle?

9 SPECIAL MASTER HASTINGS: Now this is Slide
10 35?

11 MS. RICCIARDELLA: Yes, Slide 35.

12 THE WITNESS: Yea. This is Slide 35, and
13 this is just looking at the chart of her head
14 circumference. Well, you can see on the left-hand
15 side as early as two months of age she actually starts
16 to be on the fringe of the chart, and this is also
17 reported by Ms. Cedillo I think in one of the medical
18 records, that it was noted at two months of age her
19 head was large.

20 Then as you follow up at six months she's
21 really way off the chart already and the subsequent
22 measurements are really suggesting that there is
23 massive abnormal brain growth at that time. You can
24 see that this pattern -- actually, I draw the red
25 line. It's not very well done, but it shows that

1 there is this increasing head circumference. It's
2 consistent with what I described before.

3 It's maximum between three months of age and
4 12 or 15 months of age and then it starts to
5 decelerate and the increase abates after that. So
6 this pattern of macrocephaly is what has been
7 described exactly in autism, and it's unambiguously
8 abnormal at that age.

9 SPECIAL MASTER HASTINGS: Let me ask again
10 on that. Slide 35, this is a standard head
11 circumference chart I assume?

12 THE WITNESS: Yes. This is what the
13 pediatricians use when you take a measurement of
14 height or --

15 SPECIAL MASTER HASTINGS: Okay. Now,
16 there's a series of seven black lines on the curve.
17 The middle one is darker than the other six. I assume
18 the dark one, that's the fiftieth percentile?

19 THE WITNESS: The dark one in the middle,
20 yes, is the fiftieth percentile.

21 SPECIAL MASTER HASTINGS: Now, what is the
22 top one? I really can't read those percentiles. The
23 top one is what?

24 THE WITNESS: Actually, I can't neither.
25 It's probably the ninety-fifth percentile, but I would

1 need to look back at the records. I think if one goes
2 back, or up, or down it's fiftieth, seventy-fifth,
3 ninetieth and ninety-fifth. That's what I would
4 suspect.

5 SPECIAL MASTER HASTINGS: All right. Okay.
6 Thank you.

7 THE WITNESS: And she's not just at the
8 ninety-eighth or ninety-ninth, she's really way off
9 the chart.

10 SPECIAL MASTER HASTINGS: All right. Go
11 ahead, Ms. Ricciardella.

12 THE WITNESS: And that was noted as well by
13 Dr. Roth in his report. He said, "I noted that she
14 has an enlarged head circumference," and he requested
15 an MRI or he wanted to do an MRI to explore that. And
16 he also mentioned in his report that an enlarged head
17 had been reported in autism, so he saw that himself or
18 herself as a sign of autism, as a correlate of autism.
19 So Dr. Roth concurs with that interpretation. Now
20 that is an objective sign which cannot be dismissed.

21 BY MS. RICCIARDELLA:

22 Q Doctor, we just saw a small clip of video.
23 Did you review other videotapes of Michelle as she
24 progressed during her first two years of life?

25 A Yes, I did. I reviewed all the videos which

1 were available to me.

2 Q And, again, why are home videos a good tool
3 of assessing signs and symptoms of autism?

4 A Because of the results. Surely it provides
5 a direct way to observe critical behavior in your
6 child, and sometimes it will be informative and show
7 like early abnormalities in communication development
8 or social development, and that's what I was trying to
9 do. When I reviewed these tapes, I looked at her
10 bigger years in the domains which define autism to see
11 if there were early signs as per the research which
12 has been described before.

13 Yes. So this is the slide I showed before.
14 It's exactly the same slide, 36, which is the home
15 video with the findings slide which again summarize
16 the type of abnormal behavior that could be seen at
17 age 12 months, okay? Again, the research is
18 concentrating on first birthday video, so as we had
19 the opportunity to have the first birthday video of
20 Michelle, I reviewed one of them.

21 The goal here is to look at it and see if
22 there is any abnormality which are matching those
23 descriptions. Before we see that tape, first I would
24 like to say that I know it's a bit difficult to review
25 all these tapes in the presence of parents who have

1 otherwise been extremely devoted to their child, and I
2 hope they are taking these as a gentle demonstration.

3 I have all the respect for them. They are
4 clearly devoted parents, and they should be commended
5 for all their effort, the parents. All this coming
6 section I hope will be not difficult for them, and we
7 have no intention to be difficult with them.

8 So before we look at that, it's useful for
9 everyone to try to portray in your mind what is the
10 first birthday typical. We have all attended like a
11 first birthday party. So you see there is a cake,
12 there is a gift, people sing.

13 What you would expect from the child, the
14 child would be excited, there will be pleasure on the
15 face of the child. The child would look at people
16 around with direct pleasure and facial expressions to
17 care givers who are around him. If the child is
18 called he would orient to the name. He would be
19 curious at exploring the toy. He would do something
20 with it.

21 He would have a lot of interactions with
22 people around. There would be a lot of showing,
23 pointing or gestures used to communicate, and you
24 would hear babble at least if not words, okay?

25 So there would be a range of communicative

1 behavior involving babble, maybe words, but some
2 production with a communicative intent directed to
3 others, and there would be interactions which will be
4 reciprocal involving eye contact, direction of affect,
5 a range of different facial expression, and expression
6 of pleasure and sharing of excitement.

7 Q Doctor, before we get to the videotapes,
8 though, when you reviewed the videotapes and you
9 selected the clips to show today did you have contact
10 with any other of Respondent's experts as to their
11 opinions of the videotapes?

12 A No. Absolutely not. I did it completely
13 alone and independently. So the other point I want
14 people to maybe remind, recall is that at this point,
15 it's compensatory strategies which have been described
16 in literature.

17 When a child is not responding or a child is
18 not engaged, often parents develop these tactics or
19 strategies like call the names of the child several
20 times or raise their voice or use a high pitch tone or
21 try to manipulate the child's face so that the eye
22 contact is actually physically organized by moving the
23 child into a particular visual field of direction.

24 So we need to look at that as well and
25 decide because it can be difficult for laypeople to

1 understand what we look at. But let's look at the
2 tape.

3 (Video played.)

4 THE WITNESS: I just want to say you might
5 need to pay attention to, happy birthday, Michelle,
6 happy birthday, Michelle, twice or three times, and
7 you will see repeatedly that when she's spoken to, she
8 doesn't orient at all, okay? She's not orienting to
9 the face, she's not looking, she's not responding.
10 That is a constant feature that we will see on and on.

11 (Video played.)

12 THE WITNESS: Up to that point, again, there
13 is happy birthday. She doesn't look. As she sings
14 happy birthday, at that point you would expect the
15 child to look to be happy and share affect, she
16 doesn't except at the end. You've seen again she's
17 been called several times, Michelle, Michelle,
18 Michelle, and she never orients.

19 (Video played.)

20 BY MS. RICCIARDELLA:

21 Q Doctor, what do we see from that video?

22 A So bring back the next slide, please. This
23 is the slide about the research findings, and if one
24 looks at Michelle and that particular sequence we can
25 see a lot of behaviors which have been previously

1 identified in research as early signs of autism.
2 Again, to summarize, I mean, she gives extremely
3 little eye contact to anyone. She doesn't look at
4 people except very briefly and then she doesn't really
5 sustain the eye contact.

6 There is no gesture, there is on pointing
7 and no showing. We didn't hear any babble, any words,
8 certainly not even any babble. Her facial expressions
9 are restricted and reduced. She doesn't join in when
10 there is excitement. So all that has been described.

11 We can see in terms of her posture that she's
12 unstable and in line with the motor delay which I
13 mentioned before.

14 And we also see a lot of compensatory
15 strategies that the care givers used, again, probably
16 without noticing them, not being aware that they're
17 moving the child in front of the camera so that she
18 would be seen or repeatedly calling her name for
19 attracting her attention, although she doesn't in that
20 particular sequence respond at all.

21 If we look at this series of symptoms that
22 look at what she meets all criteria, not criteria, but
23 she has all the symptoms that we could see on that
24 particular birthday video. So if she was in one of
25 these studies she would clearly be, and I could say

1 that autism experts seeing this video would have the
2 concerns that I have.

3 SPECIAL MASTER HASTINGS: Well, before we go
4 on to another one I'll just note for the record that
5 in the segment of videotape we just viewed at the
6 beginning of it it had the identification of the date
7 as August 30, 1995, and the scene was one scene I
8 think. It involved a very large box with wrapping
9 paper on it that was removed during the scene, and
10 that was basically the entire scene.

11 Go ahead.

12 BY MS. RICCIARDELLA:

13 Q The next video you want is from age eight
14 months. Is that correct?

15 A So this is one of the first video which is
16 available.

17 SPECIAL MASTER HASTINGS: Now you're looking
18 at Slide No. 40 right now. Go ahead.

19 THE WITNESS: Yes. It's a video clip which
20 is dated May 25, 1995. She's age eight months. Here
21 you will see again the behaviors to evaluate. How
22 much attention she pays to people around her, how much
23 eye contact she gives, is she interested in social
24 stimuli or does she prefer other kinds of activity?
25 Hand movements and leg movements are interesting to

1 look, and what interests her and what fascinates her
2 is also quite typical. So let's go.

3 BY MS. RICCIARDELLA:

4 Q Before we start that, Doctor, on this Slide
5 40 you have behavioral change when Sesame Street
6 starts. What do you mean by that?

7 A That she's clearly getting very sort of
8 excited when Sesame Street starts and start to have
9 hand flapping movements, which are quite repetitive,
10 and I think it's on that video that she's expressing
11 some distress when she's waiting for Sesame Street to
12 coming up some. But I need to review the video with
13 you.

14 (Video played.)

15 THE WITNESS: So here the mother says before
16 she's expecting Sesame Street, she knows it's coming,
17 and then there are two sounds that we heard were like
18 signs of unease because she wanted Sesame Street to be
19 on, and that's what the mother interprets correctly.
20 I think that she wants Sesame Street to be on the
21 screen. So let's go.

22 (Video played.)

23 THE WITNESS: In the clip you see how she's
24 fascinated by Sesame Street, that she's expecting and
25 then her behaviors change Sesame Street is on. She

1 gets very excited. We see all this sort of overflow
2 movement, also hand movements, which are like flapping
3 and stereotypic, which are clear. She doesn't at any
4 point in that sequence try to look. She looked on the
5 side, mother speaks to her, but she's oblivious to
6 comments or calls by her mother.

7 We don't hear any babble or any sign of it.
8 She doesn't direct any comments or signs of joy to
9 anyone. She's engrossed into looking at Sesame
10 Street. Just want to make this comment. Now, there
11 are so many tapes or sequences where everything is
12 about Sesame Street. Since the age of eight months up
13 to the age of 15 months the only thing which seems to
14 be attracting her or exciting her is watching Sesame
15 Street video.

16 This behavior which is a fixation on Sesame
17 Street is there very early.

18 BY MS. RICCIARDELLA:

19 Q The next clip as reflected in Slide 41 is a
20 clip of Michelle when she was nine months old taken on
21 June 4, 1995.

22 A Yes. This will just indicate again the fact
23 that when someone approached her to give her something
24 she doesn't give eye contact. What she does with the
25 toy here is typical for what we see. Across the board

1 she doesn't play with toys in a normal way, she
2 doesn't throw toys, she doesn't knock them to make
3 noise, she just mouths them.

4 That's what basically she does most of the
5 time with toys that she holds in her hand. Then there
6 are also comments by mother which are on this slide
7 which suggest that mother notes that there is
8 something which is unusual in her behavior.

9 (Video played.)

10 THE WITNESS: She doesn't make any noise,
11 she always quits talking when I turn that on. Okay.
12 So, again, indicating that it's an observation. I
13 don't think Ms. Cedillo was necessarily worried or
14 concerned, but she made that observation that she's
15 quiet, she's silent, she doesn't direct any sounds to
16 anyone, when she received the toy she doesn't give eye
17 contact, there is no sound production in that young
18 child.

19 She seems to be fascinated by nonsocial
20 stimuli, and that's what mother comments upon when she
21 says she quits talking when I turn this on.

22 BY MS. RICCIARDELLA:

23 Q The next slide, Slide 42, we're going to
24 review a video taken in the shower at nine months.
25 That was June 20, 1995.

1 A Again, there is the Sesame Street sort of
2 fixation that will be clear. Now, what is important
3 to see here is that it's really a strong engrossment
4 into that which excludes to pay attention to social
5 stimuli. So this child who is watching TV was just
6 interested, if you come in and say hey, hello, they
7 would stop or they would take into account what's
8 happening around them. She does not.

9 So in spite of, she doesn't pay attention,
10 she doesn't look at people. We don't hear much sound
11 production, but you will see that the few babbled
12 sounds that we hear have a very odd quality. They are
13 guttural and they are not the babble sound that babies
14 use to communicate or to direct to other. It's self-
15 directed, it has no communicative intent and the
16 quality, you will see, is typical or abnormal.

17 (Video played.)

18 THE WITNESS: That's it. Again, this
19 repetitive flapping movements and, again, very little
20 attention to father or mother. When mother talks she
21 is really engrossed into the watching of Sesame
22 Street, again, a feature which is consistent across
23 videos. The few sounds which are heard in these
24 videos are not directed to someone. They are somewhat
25 odd, and guttural and not indicative of communicative

1 intent.

2 BY MS. RICCIARDELLA:

3 Q So finally, Slide 43.

4 A Yes. This is probably the last one. It
5 will be a bit longer. This is 15 and a half months,
6 it's December 17, 1995, it's Slide 43. Then you have
7 a list of behaviors which I noted for you to see.
8 Okay. So let's go and see. And we have seen that
9 scene last week as well.

10 (Video played.)

11 THE WITNESS: So here, again, she's 15
12 months and a half. There is no word at all which is
13 uttered by her during this sequence, and it's not only
14 this one but throughout. We just heard a few babbling
15 sounds which are, again, guttural, not directed to
16 others, directed to herself. We see flapping
17 movements of the hand.

18 With the balls, which are the gift that she
19 received from her grandpa I believe on that day, she
20 doesn't do anything. She doesn't explore them, she
21 doesn't send them away or play with them in sort of a
22 way. She does approach her father through this kind
23 of neck but it's shortly, and she doesn't give much
24 eye contact otherwise.

25 Then soon you're going to see something

1 which is even more typical of autistic behaviors.
2 Children with autism often have these very typical
3 stereotyped hand and finger movement whereby they move
4 their fingers in their visual field like this and they
5 are absorbed by that. They do that. It's seen in
6 different circumstances.

7 You're going to see that I think in nine
8 seconds, or six seconds, whatever, that there is a
9 three second movement which is very typical. I think
10 what precedes, her mother calls her, she doesn't
11 respond, she engages in the stereotypic, as you will
12 see.

13 (Video played.)

14 THE WITNESS: Here it is. Okay. So, again,
15 when you observe what she does with the balls, I mean,
16 she doesn't do much. She takes one at one point, but
17 she doesn't play with the balls. A child of her age
18 should play with toys that she's given. We again
19 heard babble sounds which are unusual and not
20 communicative.

21 What also is quite obvious is that as most
22 parents do at that age they are very engaged and they
23 try to engage her in multiple ways which are quite
24 remarkable in some ways, but you could see that she's
25 largely unresponsive because when mother calls her she

1 has to repeat several times the same thing with a loud
2 voice, and Michelle does not to a large extent respond
3 to her mother calling her.

4 You're going to see now in a few seconds
5 another episode of this unusual hand and finger
6 mannerisms in front of her visual field. The sequence
7 is the same. Mother calls her, Michelle does not
8 respond, she engages in the therapy, produce a very
9 odd, self-directed guttural sound, engages in the
10 therapy again and then it continues. It's very quick,
11 but it's very typical.

12 (Video played.)

13 THE WITNESS: So, again, I mean, that's just
14 a continuation of the previous observation. You've
15 seen these unusual hand and finger mannerisms which
16 are again quite typical. No normal play with toys. A
17 general lack of orientation to her name being called.
18 Rocking from side to side. Flapping of the hands.
19 So I'll stop here.

20 BY MS. RICCIARDELLA:

21 Q Actually, before you continue, Dr. Fombonne,
22 did you see early signs of autistic behavior in other
23 video clips of Michelle that you reviewed?

24 A Yes. This is a sample that I observed in
25 multiple clips which are all consistent. In other

1 words, it's not a highly selected series. All the
2 videos show the same type of behavior.

3 Q And did you and I have a discussion and
4 decide to only show a few of those video clips here
5 today?

6 A I'm sorry?

7 Q Did you and I have a discussion and we
8 decided to only show just a few of those video clips
9 today?

10 A Yes, yes, yes. We could have seen more,
11 yes.

12 MS. RICCIARDELLA: Special Master, out of
13 sensitivity to the Cedillo family, we decided to only
14 show a few of the video clips that Dr. Fombonne
15 identified. If the Court would like further
16 assessment on the issue with videotaped evidence, we
17 are willing to have Dr. Fombonne walk through it
18 either in Court or in camera.

19 SPECIAL MASTER HASTINGS: All right. That
20 will be fine. You show the ones you want to. I'll
21 note for the record that in the last group of clips
22 there that were from December 17, 1995, all those
23 clips were of Michelle in a kind of tent-like device
24 full of balls that she was playing with at times, and
25 her father was in the background or on the side

1 throughout that clip.

2 Go ahead, Ms. Ricciardella.

3 BY MS. RICCIARDELLA:

4 Q The next slide, Slide 43, did you review
5 the --

6 SPECIAL MASTER HASTINGS: No, we're on 44,
7 are we not?

8 MS. RICCIARDELLA: Excuse me, 44.

9 THE WITNESS: So, yes. Before trying to
10 summarize the information that we've seen through the
11 video, I just again looked at what Mrs. Cedillo
12 mentioned last week in her testimony. Again, it's not
13 meant to be challenging what she says or believes.
14 But what she said was that after the MMR, she was
15 clearly seeing that then, only then she played
16 differently. Then she was withdrawn and quiet. Then
17 she didn't give eye contact, all the excerpts from her
18 testimony.

19 Then she stopped pointing, she became
20 engrossed in Sesame Street after the MMR, she started
21 flapping her hands, she did not respond to her name,
22 she lacked vocalization and speech.

23 So all the argument that her behaviors
24 changed and the autistic symptoms emerged after the
25 MMR vaccinations are completely not in line with what

1 we see in the video which show that all these
2 behaviors in fact were present before the MMR
3 vaccination. The only way we can summarize this
4 behavior is as follows.

5 When we've looked at them, it might be a
6 disjointed set of abnormal behaviors, but the way we
7 combine them is when I looked at all the videos,
8 including the last one, which is 15 months and a half,
9 a week or days before the onset, there was nowhere in
10 this long sequence, nowhere at all, and the babble was
11 limited in amounts and odd in quality.

12 So there was no language at all in all the
13 tapes I reviewed, not a word. There was very little
14 babble throughout. It was again lacking the
15 communicative quality that we would like to have. I
16 couldn't see any gesture. There was no pointing, no
17 showing or very few exceptions.

18 There was one instance where she did delay
19 the imitation of clapping her hands following her
20 grown father's initiations, but it was very delayed
21 and she could not repeat the imitation. This is the
22 only gesture which I see. Otherwise, there is a
23 procedural gesture. And again, portray a child of 15
24 months in your mind and you will see that. In the
25 last video clip, she's clearly not developmentally at

1 her age.

2 SPECIAL MASTER HASTINGS: Now we're on Slide
3 No. 45, are we not?

4 THE WITNESS: Yes.

5 SPECIAL MASTER HASTINGS: Go ahead.

6 THE WITNESS: So I'm trying to put these
7 observations based on video analysis into a cohesive
8 format. What we see here is not only the delay in
9 language but also the lack of compensation of lack of
10 language by gestures or by other means to communicate.
11 This is the type of communication and language
12 deficit that we see in autism spectrum disorder.

13 So these are for one domain, but there is
14 also another domain which is clearly affected in her
15 development early including the fact that she very
16 rarely orients to her name being called. We see how
17 many attempts the mother has to do to capture her
18 attention.

19 She doesn't give the right amount of eye
20 contact, she doesn't pay attention to the faces in
21 situations, her facial expressions are reduced and she
22 tends to not share affect or direct affect as part of
23 normal social interchanges. These are the types of
24 abnormalities which we call social deficits as part of
25 autism spectrum disorder.

1 Then the third domain is that, the mouthing
2 of toys. She lacks play skills which are commensurate
3 to her age. It might not be a specific sign of
4 autism. It's mostly that at 15 months of age, she
5 functions like a much younger child. She's mouthing
6 toys. She doesn't play with toys because she's
7 developmentally delayed. It speaks to her mental
8 retardation rather than to autism per se.

9 What is unusual and what is autistic is the
10 fact that she's flapping her hands, she has this odd
11 hand and finger mannerism that we've seen at the end,
12 and she has clearly since age eight months a very
13 unusual fixation on Sesame Street which excludes other
14 kinds of play and social pursuits which would be more
15 appropriate to her age.

16 As mother and others said, Sesame Street
17 became a very significant autistic behavior identified
18 as such by them later on, but it's very clear that
19 it's there much before and actually starting very
20 early. So the settled behavior corresponds to the
21 repetitive behaviors that we see in autism. We cannot
22 account for this pattern of abnormal behavior other
23 than to actually invoke an autism spectrum disorder.

24 There is no simple explanation. It's not
25 mental retardation. The global developmental delay do

1 not explain that and along with other disorders which
2 they would not explain that. This set of findings
3 based on video analysis is very consistent with an
4 autism spectrum disorder. I have no doubt in my mind.
5 When I see that child she is very abnormal and shows
6 very clear signs of both global developmental delay
7 since the beginning, and she has also clear autistic
8 type behavior.

9 If anyone sees this video, a child
10 neurologist or developmental pediatrician, they would
11 have the same concern that I express here. So for me
12 the evidence is there combined with the macrocephaly,
13 the evidence in the record, and the lack of language
14 progression, and the fact that the macrocephaly as I
15 said and something else which I forgot.

16 So all the four points I made before really
17 clearly suggest the abnormal development much before
18 the MMR injection.

19 BY MS. RICCIARDELLA:

20 Q I think you just answered my next question.
21 Petitioners have presented Michelle as entirely normal
22 before her vaccination. I take it you do not agree?

23 A No, I do not agree with that explanation.

24 Q And Petitioners have presented Michelle as
25 having lost skills following her MMR vaccination. Do

1 you agree?

2 A Actually, no, I do not. Based on the review
3 of the video I would not agree that Michelle has
4 actually lost skills. It's very clear that the
5 account of a loss of skills in her medical history is
6 based on the assumption that she was using 10 words,
7 that she lost subsequently. Based on the analysis of
8 the lab videos and the sessions which precede the MMR,
9 you see the last session there is absolutely no word
10 used by this child.

11 So she might have well said in imitation
12 five, six words once occasionally, but she didn't
13 acquire these words, and therefore it's hard to assert
14 that she actually lost them.

15 In my previous report, in my original
16 report, because there was this notion that she was
17 using 10 words I accepted that she might have
18 experienced a loss of skills, although the early
19 development was abnormal anyway, but based on this
20 video analysis I would actually dispute the fact that
21 she has regressed because it's very clear that her
22 communicative skills at 15 months and a half are
23 really far behind.

24 There is no language or enough language to
25 be lost as part of regression in autism.

1 Q Doctor, when you were discussing page 15 of
2 your slides entitled Developmental Trajectories in
3 Autistic Spectrum Disorder you distinguished between
4 early onset, fluctuating skill acquisition, regression
5 and childhood disintegrative disorder. Which subtype
6 do you believe Michelle falls under?

7 A She falls into the early onset category. As
8 early as eight months of age we can see both a delay
9 and abnormal qualities in her development, so she
10 falls into that group of early onset autism.

11 Q Now, Doctor, assume for purposes of my next
12 question that Michelle is indeed a case of regressive
13 autism. Does that mean, though, that her development
14 was entirely normal before her regression?

15 A I'm sorry. Could you repeat the question?

16 Q Certainly. Assume that this is a case,
17 indeed of regressive autism, that you are convinced
18 that this is a case of regressive autism. Does that
19 mean that Michelle's development would have
20 necessarily been normal up to the point of loss of
21 skills?

22 A No, no. That was as per my report when I
23 was accepting there will be a language loss at that
24 stage. I also pointed out the fact that she had a
25 clear abnormal development before. Research showed

1 that 50 to 70 percent of children who have this loss
2 of skill sometimes in the second year of their life
3 were in fact abnormal earlier before the loss
4 occurred, so it doesn't affect my assessment.

5 Q Now, Doctor, you testified earlier that in
6 your opinion Michelle's receipt of thimerosal
7 containing vaccine and the MMR vaccination did not
8 cause or contribute to her autism. Is that correct?

9 A Yes, it's correct.

10 Q Now, assume again that this is indeed a case
11 of regressive autism, that you are convinced that she
12 lost skills, would your opinion in this case be
13 different?

14 A No. Based on the existing body of evidence
15 that we have, absolutely no.

16 Q Now, there's been some talk in this case
17 about Michelle may or may not have inflammatory bowel
18 condition. Is the presence of an inflammatory bowel
19 condition in Michelle an important factor in your
20 opinion in this case?

21 A No, it is not. It doesn't inform my
22 evaluation of the question about the links between
23 immunization and autism. Autistic children can have
24 all sorts of medical conditions. Autism does not
25 protect against inflammatory bowel disease.

1 It can occur in a child in addition to
2 autism as a co-occurring condition, and there are
3 actually several studies which have looked at the risk
4 of IBD or inflammatory bowel disease in autistic
5 children that have not shown any increase in the risk
6 of IBD in children with autism.

7 So in my opinion, the bowel disorder is
8 irrelevant to the assessment of causality regarding
9 autism. It's just a completely co-occurring medical
10 feature which involves that management but not from an
11 etiologic perspective.

12 Q Doctor, we've spent the morning talking
13 about autistic spectrum disorders in general. Why
14 have you devoted your life's research to autistic
15 spectrum disorder?

16 A I do research in other domains as well, so
17 my life is not entirely devoted to that. It's true
18 it's a very captivating, should I say, disorder, and
19 it's clinically something which is quite moving.

20 I mean, the experience to have an autistic
21 child is something which, you know, a child is
22 affected in what is the core aspect of our human
23 condition, which is social relatedness, and that is
24 something which is a powerful motivation for all of us
25 who are autism experts to try to unravel the causes

1 and improve the management, and we are committed to do
2 that the best we can using scientific methods.

3 MS. RICCIARDELLA: At this time, Special
4 Master, I have no further questions of Dr. Fombonne.
5 We indicated last week we do intend to bring Dr.
6 Fombonne back later on in our case since he is to
7 speak specifically about epidemiology in autism.

8 SPECIAL MASTER HASTINGS: I understand. I'm
9 thinking we should probably break for lunch before
10 cross, but before we do let me first comment -- you
11 may sit down, Ms. Ricciardella -- just very briefly to
12 Mr. and Ms. Cedillo who are with us and have been with
13 us throughout all the testimony, and they tell me they
14 intend to stick with us throughout the whole time. I
15 thank them again for their presence and apologize that
16 we have to put you through this watching the videos.

17 Obviously, Michelle was an extremely
18 adorable child in these videos, and in fact they
19 showed today I think some of the same ones that your
20 attorney showed while you were testifying, Ms.
21 Cedillo. Again, we're sorry to have to put you
22 through this. There is some information that may have
23 a bearing on the causality issue that's going to be
24 before me, so we have to look at these.

25 I want to ask one question right now, just

1 one, to Dr. Fombonne maybe for the benefit of the
2 Cedillos and for any other parents who may be
3 listening in.

4 Dr. Fombonne, my question is this. You
5 know, you went through those videos, and in your
6 opinion with the benefit of hindsight looking at these
7 videos and knowing what Michelle's course has been to
8 today you looked back with the benefit of hindsight
9 and saw that in May, and June and August of 1995 you
10 see behaviors that you feel were definitely with the
11 benefit of hindsight indicative of autism. Is that
12 correct? Did I correctly summarize your testimony?

13 THE WITNESS: Yes. Of course I was aware of
14 the diagnosis of Michelle, so I didn't rate, view
15 these videos blindly if this is what you mean.

16 SPECIAL MASTER HASTINGS: Well, here's the
17 question for you. You're not suggesting, are you,
18 that the parents should have known at the time that
19 their child was abnormal and should have sought more
20 medical attention at that time? You're not suggesting
21 that, are you?

22 THE WITNESS: No, not at all. I might
23 express some different analysis of the material which
24 is presented, but I'm not disputing the testimony of
25 Ms. Cedillo or her husband. Again, they are devoted

1 parents and I have no comments to make about what
2 happened in the early years of Michelle. It is common
3 experience that parents do not pick up the
4 abnormalities.

5 They shouldn't blame themselves for having
6 not done that. It's not at all what is on the agenda.
7 We however often see parents who start to identify
8 the presence and then with hindsight they would
9 identify the cause, but it's very clear. Actually, we
10 have research. On the research study which I showed
11 we looked at one factor which predicts the age at
12 which parents recognize the first symptoms of autism
13 in a child is the fact that whether or not they have
14 other children.

15 So those who have had a child already
16 usually are quicker to pick up the abnormalities
17 because they have a template for normal child
18 development. When it's the first born child on
19 average there is a two or three month gap for
20 recognizing the first developmental abnormalities in
21 research terms.

22 So it's not surprising that many parents,
23 especially when they don't have experience of a
24 previous typically developing child, it would take
25 more time for them to pick up the abnormalities. But

1 irrespective of that parents will pick up the
2 abnormalities at one point in time and often there
3 would be subtle abnormalities before that would escape
4 their attention.

5 You can see that they are actually
6 compensating in their behavior the lack of response in
7 the child, but they are not aware of that. So there
8 is no idea here to ascribe any intentionality or any
9 kind of wrong behavior or we should have done that,
10 not at all.

11 SPECIAL MASTER HASTINGS: All right. Thank
12 you, Doctor. I appreciate that. With that, we're
13 going to take a break. It's about 10 minutes to 1.
14 We'll convene again about 10 minutes to 2:00.

15 (Whereupon, at 12:48 p.m., the hearing in
16 the above-entitled matter was recessed, to reconvene
17 this same day, Monday, June 18, 2007, at 1:50 p.m.)

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1 Q And the section that's specific to Michelle
2 begins at approximately page 52?

3 A Yes.

4 SPECIAL MASTER HASTINGS: Let me see, Ms.
5 Chin-Caplan. How about the mark for you? We want to
6 make sure the people at home can read it.

7 THE WITNESS: Yes.

8 SPECIAL MASTER HASTINGS: Very good, it
9 sounds like we've got everything.

10 MS. CHIN-CAPLAN: Certainly.

11 THE WITNESS: Yes.

12 BY MS. CHIN-CAPLAN:

13 Q So the last 10 pages of the report involve
14 Michelle?

15 A Yes.

16 Q And the previous 52 pages involve
17 epidemiological work that you've been involved in. Is
18 that true?

19 A Portions. The pages which concern the
20 severe ones are at the beginning, I think. So there
21 was general sections on autism.

22 Q Doctor, your position is that Michelle
23 demonstrated early signs of autism?

24 A Yes.

25 Q And you based it primarily on the handout,

1 page 32, and you summarize it as evidence of early
2 before-MMR abnormal development?

3 A Yes.

4 Q Doctor, one of the things that you base your
5 assessment that Michelle had early autism is that she
6 had an abnormal brain growth, as indexed by
7 macrocephaly. Is that true?

8 A Yes, it's was one of indices of early
9 abnormal development in her case, not the only one,
10 but it's one of them.

11 Q Doctor, you're a psychiatrist, am I correct?

12 A Yes.

13 Q A pediatric psychiatrist.

14 A Yes.

15 Q And when a physician looks at a child's head
16 size, don't they normally compare it to both the
17 weight and the length of the child?

18 A Yes.

19 Q And would you expect to see comparable
20 growth in all those three areas?

21 A Well, there is a relationship between body
22 length and head circumference, more than with weight.
23 So yes, it is something that you need to take into
24 account.

25 Q And what you would expect to see if a child

1 was having some development problems is the head size
2 growth is not comparable to the rest of the body. Is
3 that true?

4 A Yes, and in autism, there have been studies
5 and the macrocephaly of the large head circumference
6 is observed, even when you take into account the size
7 and the height.

8 Q Doctor, I'd like to take a look at this
9 slide. For the Court, it is Petitioner's Exhibit 70,
10 page nine and ten.

11 SPECIAL MASTER HASTINGS: Thank you.

12 BY MS. CHIN-CAPLAN:

13 Q Doctor, if you would just follow along,
14 please. On the right hand size, there is a section
15 that says, "Head Circumference." Is that true?

16 A Yes, sure, on the right hand side? Yes.

17 Q On the right hand side?

18 A Yes.

19 Q This is what you showed the Court, isn't it
20 true, on your slide presentation?

21 A Yes, that's correct, yes.

22 Q And on the left hand side of this, it
23 indicates length and weight of the child. Is that
24 true?

25 A Yes.

1 Q Doctor, your point was that Michelle
2 exceeded, I think, roughly the 95th percentile on her
3 head size. Is that true?

4 A Yes.

5 Q Now if you take a look at her length and her
6 weight, was there comparable growth in the length and
7 weight?

8 A The weight is comparable. Growth is not
9 even actually -- no growth in the head circumference,
10 but the length has actually a slightly lower deviation
11 from the norm than the head circumference. So when
12 you take that into account, there is still a large
13 head.

14 Q Okay. But it's clear that she's continuing
15 to grow and she's getting longer, and she's gaining
16 weight, correct?

17 A Yes.

18 Q Doctor, by the way, you didn't show the
19 length and the weight to the Court, did you? You just
20 showed the head size.

21 A Yes, correct, but I think in my report, I
22 mentioned that it could not be accounted by her body
23 length, if I recall well.

24 Q Doctor, is it your opinion that the head
25 size alone is indicative of early signs of autism? Is

1 that it, and you don't take into consideration the
2 length and weight of the child?

3 A No, you usually do not consider that. You
4 don't take into account the weight of the child,
5 because head circumference is related to body length.
6 So studies have shown that when you adjust for the
7 height of the child, there is still a tendency for the
8 head to go at a higher rate than the body length.

9 What Michelle's chart shows is exactly that
10 there is certainly an increased rate of growth in
11 terms of her height. But the growth of the head is
12 much higher. The speed of the growth of the head is
13 much higher than that of her body size.

14 Q Doctor, are you familiar with Dr. Andrew
15 Zimmerman?

16 A Do I know him?

17 Q Yes, do you know him?

18 A I know who he is. I don't know him
19 personally.

20 Q Okay. He was scheduled to testify.

21 A Yes.

22 Q He submitted a report, and I would ask you
23 to take a look at Respondent's Exhibit F, page five.
24 Do you have it?

25 A Do I have it?

1 Q Can you show me?

2 SPECIAL MASTER HASTINGS: Can you give him a
3 copy?

4 MR. MATANOSKI: We didn't expect him to be
5 cross examined on someone else's report. We expected
6 him to be examined on his report.

7 MS. CHIN-CAPLAN: Then I will look over his
8 shoulder.

9 BY MS. CHIN-CAPLAN:

10 Q Dr. Fombonne, on page five of Dr.
11 Zimmerman's report, he also talks about rapid
12 acceleration of head growth. Is that not true?

13 A Yes.

14 Q And he also indicates, it has been
15 documented during early post-natal development. Is
16 that true?

17 A Yes.

18 Q But then he adds, but not height or weight,
19 the causes of which are still unknown?

20 A Yes.

21 Q I've read that correctly?

22 A Yes.

23 Q Doctor, continuing on with your report, you
24 give a brief history of what happened to Michelle
25 immediately after the MMR. Is that true?

1 A I'm sorry, could you repeat?

2 Q You gave a brief history of what happened to
3 Michelle after her MMR.

4 A I don't think I gave a brief history of
5 that. Could you specify what you mean?

6 Q Sure, if you look on page 57 of your report,
7 you documented some history from Dr. Roth. Is that
8 true?

9 A So where are you look on that page?

10 Q Paragraph 151.

11 A Paragraph 151, yes, okay.

12 Q It's just a very brief history, isn't it,
13 kind of documenting what had occurred to Michelle?

14 A Yes.

15 Q By Dr. Roth?

16 A Yes.

17 Q Doctor, when you reviewed the medical
18 records, did you notice that Michelle had had a very
19 high fever after the MMR?

20 A Yes.

21 Q And it was roughly 105, almost 106?

22 A Yes.

23 Q That occurred approximately one week after
24 the MMR. Is that true?

25 A Yes, from what I recall, yes.

1 Q Are you familiar with MMR at all, and
2 specifically the measles component?

3 A Well, I'm not a virologist, and I'm not an
4 infectious disease physician. But I know MMRs, as
5 many doctors and parents, yes.

6 Q But you have some general knowledge.

7 A Yes, sure, of course, yes.

8 Q So from your general knowledge, are you
9 aware that the measles component is a strong
10 immunosuppressant of the immune system?

11 A No, I'm aware that the vaccine in the MMR
12 vaccine leads to immunosuppression. I'm not an
13 immunologist, so I would defer these questions to
14 other experts in that case.

15 Q Okay. So you don't know that the immune
16 suppression begins approximately one week after
17 administration of the vaccine?

18 A My knowledge of this aspect is limited. I
19 would not offer an opinion on that.

20 Q Then you don't know also that the nadir of
21 that immunosuppression is sometimes in the four to six
22 week range?

23 A Again, I have no opinion on that particular
24 question.

25 Q Do you know that during that period of

1 immunosuppression that children are prone to
2 opportunistic infections?

3 A I understand what you say, and I have no
4 particular knowledge of studies which show that, no.

5 Q So when Michelle developed her second fever,
6 which was approximately two days after the first one
7 ended, about January 5th I believe --

8 A Yes, that's more like five days.

9 Q Did you finish your answer?

10 A It's about five days after the first fever,
11 as I understand, or even more than that.

12 Q Okay. So would that fall within the period
13 when she was immunosuppressed?

14 A I have no evidence that she was
15 immunosuppressed at that time. If you provide some
16 such data, I think that can be reviewed by competent
17 people.

18 Q Do you know the period of maximum viremia
19 after exposure to measles?

20 A No, I don't recall that off the top of my head.
21 I think it's a few days, five days, I think, after
22 the injection, but I'm not even sure. It's probably
23 six to five days.

24 Q But if I represented to you that the period
25 of maximum viremia is somewhere within a seven to

1 fourteen day period, would that sound right to you?

2 A Again, I have no expertise in the field of
3 virology, and I have no professional opinion to offer
4 on that question.

5 Q But you have no reason to doubt it, right?

6 A I'm sorry. Again, it's not something I have
7 reviewed and read about. So I think I have no opinion
8 that I'm prepared to offer at this point in time.

9 Q I have one last question on this.

10 A Yes.

11 Q The fevers that she suffered at
12 approximately one week after the immunization and the
13 subsequent fever as well, if you assume the period of
14 maximum viremia is roughly seven to fourteen days,
15 would Michelle's fever have occurred within that
16 period of time?

17 A Again, I have no opinion regarding the fever
18 and the course of immunization. So core current
19 infections, immunosuppressions, this is not my field
20 of expertise. What I can just say is that there is no
21 known association between fever and immunosuppression
22 and autism. That's what I think we can say.

23 Q Now, Doctor, you don't dispute the timeframe
24 in which Michelle received her actual diagnosis of
25 autism, correct?

1 A What do you mean by the timeframe that she
2 received her diagnosis?

3 Q When she was first diagnosed with autism.

4 A No, there is no dispute. She was diagnosed,
5 as I recall, in the Summer of 1997, shortly before she
6 was age 3, by Dr. Roth.

7 SPECIAL MASTER HASTINGS: Could you keep
8 your voice up a little?

9 THE WITNESS: I'm sorry. I'm sorry.

10 BY MS. CHIN-CAPLAN:

11 Q Doctor, you don't dispute either the
12 timeframe in which the gradual change in Michelle's
13 communication skills were noted, do you?

14 A Could you explain your question? Because if
15 there is a dispute, there should be different
16 arguments.

17 Q Sure.

18 A And I don't understand what you mean.

19 Q Sure, the record documents that sometime
20 between January 1996 and March 1996, Michelle lost
21 words. You don't really dispute that, do you?

22 A No, I think the records show that Mrs.
23 Cedillo went to her doctor on I think the 15th of
24 March or early March 1996. This is when there is
25 documentation in the medical records that mother was

1 concerned about the loss of words in Michelle in
2 previous weeks.

3 There are other professional reports which
4 mention the onset or recognition of first symptoms by
5 the parents sometime between January and March it is
6 said in several places initially, including, I think,
7 in Mrs. Cedillo's narrative, which is dated 1997 or
8 1998, or something like that.

9 Q So we can agree that sometime between
10 January or March of 1996, Michelle lost words.

11 A I would be more cautious about this last
12 part of your statement. As I said earlier, the review
13 of the videos gives sort of new light about the extent
14 to which we had actual language before the MMR
15 vaccinations, or before December 20th.

16 As I reviewed the tape this morning, the
17 tape dated the 17th of December shows no single words
18 whatsoever, and there was no use of words at all in
19 all the video evidence that we reviewed. So whether
20 she lost words in the weeks which followed, I think is
21 very hard to estimate.

22 Q But you would agree that her March 1996
23 pediatric record says, "Last words since illness in
24 December"?

25 A Yes. In the medical record, mother reports

1 to the doctor that she lost words.

2 Q So you would agree with that?

3 A Yes, sure.

4 Q Now, Doctor, you've written numerous
5 articles. Is that true?

6 A Yes.

7 Q Some were on epidemiology, some on other
8 topics.

9 A Yes.

10 Q Doctor, did you write an article that looked
11 at the reliability of a primary care physician when
12 they needed a diagnosis of autism?

13 A Off the top of my head, I would say no.
14 Primary care physicians --

15 Q Give me a minute.

16 SPECIAL MASTER HASTINGS: Do you know the
17 tab number, Ms. Chin-Caplan, or does anyone?

18 MS. CHIN-CAPLAN: I have the article
19 printed. Let me see if I can find it.

20 SPECIAL MASTER HASTINGS: Okay. Does anyone
21 happen to know so I can find it while you're looking?

22 MS. CHIN-CAPLAN: It's entitled, "Pervasive
23 Developmental Disorders in Preschool Children:
24 Confirmation of High Prevalence."

25 THE WITNESS: Oh, yes.

1 SPECIAL MASTER HASTINGS: Does anyone know
2 where it is in the record? That's what I'm asking.
3 I'm asking anyone in the courtroom.

4 (Laughter).

5 MS. CHIN-CAPLAN: It's Petitioner's Exhibit
6 P, Tab 26.

7 SPECIAL MASTER HASTINGS: Thank you.

8 MS. CHIN-CAPLAN: You're welcome.

9 SPECIAL MASTER HASTINGS: Go ahead. I've
10 got it. Go right ahead.

11 BY MS. CHIN-CAPLAN:

12 Q Doctor, do you have that?

13 A No, I know what you're referring to now, but
14 I don't have the articles. It's the *American Journal*
15 *of Psychiatry*. No. No, that should be the *American*
16 *Journal of Psychiatry*. I think so.

17 SPECIAL MASTER HASTINGS: This is an article
18 by Lee Stefano.

19 MS. CHIN-CAPLAN: No, Special Master.

20 SPECIAL MASTER HASTINGS: Then it's not Tab
21 26, I don't think.

22 MS. CHIN-CAPLAN: It's Attachment 26.

23 SPECIAL MASTER HASTINGS: I'm sorry?

24 MS. CHIN-CAPLAN: I have it as Attachment
25 26.

1 SPECIAL MASTER HASTINGS: Tab?

2 MS. CHIN-CAPLAN: Twenty-six.

3 MALE VOICE: Petitioner's Exhibit P,
4 Attachment 26.

5 MS. CHIN-CAPLAN: No, Respondent's --

6 SPECIAL MASTER HASTINGS: Respondent's
7 Exhibit P -- I'm looking at Respondent's Exhibit P,
8 Tab 26.

9 THE WITNESS: This is *AJP, American Journal*
10 *of Psychiatry*, line 5, Chakrabarti.

11 SPECIAL MASTER HASTINGS: And I'm seeing an
12 article by Lee Stefano, et al, called "Aid to First
13 Measles, Mumps, Rubella." Okay. Thank you. Okay.
14 I've got it.

15 BY MS. CHIN-CAPLAN:

16 Q Doctor, I'm going to ask you to take a look
17 at page 1136 of this article, and the section on
18 Reliability Study.

19 A Which section?

20 Q Reliability Study?

21 A Reliability, yes, yes.

22 Q Yes, and the very last sentence --

23 A Yes.

24 Q -- have you read it?

25 A I read it, yes.

1 Q So, Doctor, just so we get this into the
2 record here, it states, "Blinded raters were also
3 asked to provide an independent global judgment about
4 the presence or absence of pervasive developmental
5 disorder, based on the parental interview, and they
6 confirmed the presence of pervasive developmental
7 disorders in all 38 children, yielding a 100 percent
8 agreement with the original pediatrician's diagnosis."
9 Have I read that correctly?

10 A Yes.

11 Q Doctor, could you just explain to the Court
12 what that sentence means?

13 A Yes, my co-author on this paper is not a
14 primary care physician. That's why I did not
15 understand what you mean. It is a developmental
16 pediatrician who has special expertise in
17 developmental disorders. So he has set up a
18 developmental center in his region where we did these
19 studies.

20 So initially, the children that were
21 identified in these two surveys, were referred by
22 general practitioners from the local area, speech
23 therapists, house visitors with the specific
24 professions in the U.K.

25 They were referred after having been trained

1 to identify the first signs of autism by him, and we
2 send them a brief on how to refer on this and which
3 kind of symptoms are shown by which children at which
4 age, and then to refer to this center where they are
5 assessed by a multi-disciplinary team.

6 It was, I think, a one week complete,
7 comprehensive assessment, in a hospital where they
8 came all day with their parents or their mother.
9 There were occupational therapy assessments, speech
10 and knowledge assessment, blood work being done, and
11 we observed.

12 Then following that, some more standardized
13 assessments were performed, using ADI in particular,
14 which is the autism diagnostic interview, the
15 standardized domestic measure referred to this
16 morning. So Dr. Chakrabarti turned to the ADI, and
17 did the diagnostic interviews on these children. He
18 had first generated a clinical diagnosis on these
19 children.

20 So after the one week assessment, they
21 concluded as to whether or not the child has one form
22 of ASD or PDD, and if he did, what was the precise
23 diagnosis. Then he collected in developmental
24 interviews, domestic interviews. Some of them were
25 videotaped. As part of our concern when we conduct

1 research about reliability, I especially wanted to
2 check the diagnosis on the subset of children which
3 were included in that study.

4 So we selected some tapes that he had
5 available, based on his autism domestic interviews,
6 video-taped. He assigned them to me, and they were
7 routed in my department, on my team, by a research
8 assistant, which were blind to the actual outcome in
9 the charge.

10 It's a long interview, so we score
11 particular symptoms. Then at the end, you have
12 different sub-scores that you can indicate. If you
13 have like, for instance, a pair of interviews as we
14 look at the same tape, you can then compare. If the
15 blindly rate incentive, you can then compare at the
16 end whether or not they agree on the score in
17 communication polling in the sociointeractions.

18 So that's what we did in the study. We
19 measured the inter-rater reliability by two blind
20 raters of the subset of video tapes, using the ADI on
21 a sub-sample of this study.

22 One of the questions which was asked at the
23 end to the research assistant was, in your opinion,
24 does that child meet with conscious effort, any
25 purpose of developmental disorder, yes or no? So they

1 are forced to make a choice.

2 All these tapes agree that the children had
3 PDD, and that was conversion with the initial
4 diagnostic impression of the pediatrician. It could
5 have been, for instance, 80 persons in other cases or
6 90 persons on other cases. Now in all cases there
7 were in agreement on the presence of a PDD in that
8 subsample.

9 Q But the pediatrician who initially made the
10 diagnosis --

11 A Yes, but that diagnosis was unknown to those
12 who rated the tapes.

13 Q Now, Doctor, you're aware that Michelle had
14 a pediatrician. Isn't that true?

15 A Yes.

16 Q And when you revealed her medical records,
17 her pediatric records, was there any indication that
18 her pediatrician thought that Michelle was
19 developmentally delayed?

20 A Not that I recall, but in later professional
21 reports, there was clearly a mention of delay in
22 several milestones, like social smiling, which is
23 related to four to six months of age, or sitting at 11
24 months of age, which she is clearly motor delayed in
25 the development. So while it is not documented in the

1 notes, it's documented later by other professionals
2 when they reviewed the developmental history.

3 Q I'm speaking specifically about her
4 pediatric record.

5 A Yes.

6 Q Was there any indication on any of those
7 well child visits that Michelle was developmentally
8 delayed?

9 A No, not by the pediatrician who saw her, up
10 to the immunization.

11 Q Doctor, one of the reasons that you believe
12 that Michelle was demonstrating early signs of autism
13 was the evidence of motor delay.

14 A Yes.

15 Q Do you remember that?

16 A Yes.

17 Q As evidence of her motor delay, you cited
18 the date 2/6/96, when she was age 17 and-a-half
19 months. Is that true?

20 A Yes.

21 Q That's on page 34 of your handout.

22 A Yes, slide 32.

23 SPECIAL MASTER HASTINGS: Slide 34.

24 THE WITNESS: Yes, sorry, the videotape,
25 yes.

1 BY MS. CHIN-CAPLAN:

2 Q That was 2/6/96, correct?

3 A Yes, correct.

4 Q That's evidence of the fact that she was
5 delayed in her walking, that video clip that you
6 showed us.

7 A This is one piece of evidence on the fact
8 that she didn't meet motor development in milestones
9 in due time. Again, she was not crawling before nine
10 months of age, not sitting independently before eleven
11 months of age, which is very late.

12 Although there is mention in some of the
13 medical records or reports that she was walking by age
14 15 or 16 months, that's what is mentioned here and
15 there. It's very clear from the video that by almost
16 18 months of age, she was not walking independently.
17 This is the continuation of previous mental delays,
18 which are well documented in the file.

19 Q You're aware that 2/6/96 is after she had
20 suffered those two fevers, aren't you?

21 A Yes.

22 Q So the fact that she was motor delayed in
23 what you're citing to as evidence of early autism,
24 occurred after the MMR?

25 A Yes, I do note this as evidence of early

1 signs of autism. I said early abnormal development,
2 which is very different.

3 Some children with autism do exhibit delays
4 in their motor muscles, but not all of them by and
5 large. The kind of delays that she has in her
6 development are more consistent with the fact that in
7 addition to her autism, she's globally developmentally
8 delayed. That speaks more to the mental retardation
9 which is documented later in our file. Mentally
10 retarded children often have this pattern of late
11 milestones in motor development, which she has.

12 Q You're saying she was globally delayed,
13 correct?

14 A Yes.

15 Q Do you see any notation in her pediatric
16 record that she was globally delayed?

17 A Yes. Yes. As I said, there are several
18 milestones that she didn't meet in time. Social
19 smiling is not there, motor delays of different types,
20 much before the MMR was administered.

21 Then I would need to consult my report, but
22 she has then been assessed with particular
23 psychometric assessments, which documented the fact
24 that she was delayed in her global development, using
25 various tests like the viamon (ph), which showed

1 scores which were under the percentile. There is a
2 consistency of evolution to make sure that she is
3 mentally retarded and developmentally delayed.

4 Q The question to you, Doctor, was did you see
5 in her pediatric records that she was globally
6 delayed?

7 SPECIAL MASTER HASTINGS: I think the reason
8 you're having a problem here is, you mean one thing by
9 the pediatric record, and he means another thing. I
10 think she's asking you, do the pediatricians ever
11 write out, "motor delay." You know, that's what I
12 think she's asking you. Do they actually conclude
13 that there's motor delay?

14 THE WITNESS: No, no, that's clear in the
15 record. I couldn't see it, at any visits which
16 preceded the last visit, which was March, 1996. But
17 pediatricians in his note or her notes did not mention
18 delays in mental development.

19 I don't recall the name. But this is
20 mentioned later, when the careful developmental study
21 was made. It is mentioned clearly that this is not
22 inconsistent with what we see all the time.

23 BY MS. CHIN-CAPLAN:

24 Q But the records that were taken
25 contemporaneously at her pediatrician's office do not

1 mention global delay, does it?

2 A No.

3 Q Now, Doctor, you indicated that there was
4 evidence of early social communicative abnormalities.

5 Do you recall that?

6 A Yes.

7 Q I was a little confused when you were going
8 through that. But I did not understand specifically
9 what you were referring to. So could you direct me to
10 your handout, where the social communicative
11 abnormality are listed?

12 A Yes, I've seen that, yes.

13 Q Where did you list them?

14 A Where do I list them?

15 Q In your slide show.

16 A Oh, what is the number of the slide that you
17 want? It's slide 32.

18 Q Slide 42?

19 A It's slide 32.

20 Q Slide 32 -- but you gave specifics about
21 what constituted early social communicative
22 abnormalities, didn't you? And could you direct me to
23 where that was in your slide presentation?

24 A I just spoke about them first, indicating
25 that she was discarded in the medical record as an

1 infant, as being very silent, undemanding, very quiet,
2 tending to be very content. These are descriptions
3 that we often see in the autism literature, when the
4 infant development is reviewed with respect to
5 activity. So this is some evidence.

6 Secondly, I said that, as I recall, I think
7 I mentioned that she was delayed in her social
8 development. She didn't smile socially before four to
9 six months of age, which is indicated in one
10 professional report of 1997, I think. That, again, is
11 a dealer in social development.

12 Then the last argument, which I put forward
13 this morning, was the fact that by 15 and-a-half, if
14 we accept that she had 10 words which would be used
15 consistently and with meaning every day, which is very
16 debatable, we have prediction, compared to knowns
17 which exists typically for developing infants in the
18 U.S., using the scale I mentioned to you, which is the
19 MacArthur Communicative Development Inventory. We
20 have knowns.

21 So we know when you're doing an average, it
22 starts to produce, whereas how many they have on
23 average, at eight, nine, ten months, up to sixteen
24 months, and onwards. Based on that, she would score
25 in the last five percentiles very easily, which

1 indicates that she was delayed in her language
2 development, based on the assumption that she had 10
3 words, which is not a very conservative assumption.

4 Q In the video that you saw, she smiled
5 several times, didn't she?

6 A Yes.

7 Q That was roughly at nine months, correct?

8 A We'd have to see. But yes, she smiles on a
9 few occasions, yes.

10 Q Okay. And do you recall the one with the
11 jungle gym at all?

12 A The what?

13 Q The jungle gym. She was sitting up in the
14 little jungle gym and she's batting a mirror?

15 A No, I don't, so I never would need to see it
16 again.

17 Q You don't remember that one at all?

18 A No, no, I don't know.

19 Q Okay.

20 A I must have seen it, because I've seen them
21 all. I'm sure if there is something to see, we could
22 watch it.

23 Q Now, Doctor, continuing on that topic, on
24 page 59 of your report, paragraph 155, you state the
25 very same thing that you stated right now, that she

1 was a good baby, cried little, awoken to be fed. She
2 seemed to be very content. She didn't smile until
3 four to six months of age, and she had about 10 words,
4 so she said mostly in imitation. That's what you
5 said.

6 A Yes.

7 Q About 10 words.

8 A That's what Dr. Hoff says in his report in
9 1997, which I copied exactly, yes.

10 Q And you accept that, is that true?

11 A Yes, that's what is in the record.

12 Q Okay. And then you go on further in that
13 paragraph. You say babies later diagnosed with autism
14 are described as less socially responsive or active,
15 and language when it develops progresses very slowly,
16 lacks spontaneity and relies on various parental
17 prompts to occur. You cite Bryson, et al, 2007,
18 correct?

19 A Yes.

20 Q And Bryson is included at Respondent's
21 Exhibit P, Tab 15, correct?

22 A I think so.

23 Q Doctor, what's the title of this article?
24 This is the article you cited to, isn't it, in your
25 report?

1 A Yes, yes.

2 Q What is the title of this article?

3 A A Prospective Case Studies of High Risk
4 Infants Who Developed Autism.

5 Q Okay. And, Doctor, in the abstract, does it
6 indicate what the article is about?

7 A I suppose. Do you want me to read that?

8 Q Certainly.

9 A Yes, okay.

10 Q Now, Doctor, in this abstract, does it
11 indicate that they came to two groups essentially?

12 A Yes.

13 Q And the first group showed a decrease in IQ,
14 between 12 and 24 or 36 months of age.

15 A Yes, correct.

16 Q And the second group continued to obtain
17 average or near average IQs.

18 A Correct.

19 Q That next sentence, Doctor, does it say,
20 "Signs of autism emerged and/or were more striking
21 earlier in the first subgroup."

22 A Yes.

23 Q "In all nine children, early impairment and
24 social communicative development co-existed with
25 atypical sensory and/or motor behaviors, as did a

1 temperamental profile, marked by irritability,
2 distress and dysregulated state." Have I read that
3 correctly?

4 A Correct.

5 Q Doctor, it then goes on to look at some of
6 these patients that they were studying, doesn't it?

7 A Yes.

8 Q Okay. And there were several children,
9 correct?

10 A Nine.

11 Q Let's go through some of them to see what
12 types of symptoms these physicians saw in these
13 autistic children. So in Case No. 1, Doctor, who is
14 on page 15, there's a diagnosis of autism made at 36
15 months, correct?

16 A Yes, yes, correct.

17 Q Okay. Now, Doctor, they seem to have
18 divided into 6, 12, 15, and 18 months. So at 6
19 months, was there anything noted in this male child?

20 A Well, they mention sort of delayed motor
21 development.

22 Q Okay. Was there anything beyond that?

23 A They mention, "Did not orient to name
24 called, but oriented to mom talking, some babbling."

25 Q Then when they get older at twelve months,

1 what did they notice?

2 A That there is a change -- at twelve months,
3 there is limited interesting pleasure in
4 responsiveness to others; brief eye contact; some
5 social smiling, more so triggered by physical
6 stimulations such as tickling; no social anticipation;
7 no anticipatory arm movement; inconsistent orienting
8 to name; and other kinds of symptoms.

9 Q Okay. And when you go on to the next
10 paragraph -- actually, it's a continuation onto the
11 next column.

12 A Okay.

13 Q Does it say in that second sentence, "Little
14 reaching for objects, flailed arms and legs in
15 reaction to toys, acted on objected without looking at
16 them, atypical sensory behaviors"?

17 As an example, it says, "Visual interest in
18 copper pad and feeling with index finger"; "Atypical
19 motor behaviors, hand flapping, and finger flicking;
20 marked delay in motor development, generally
21 hypertonic, but rigid when standing with assistance;
22 seemed uncomfortable when being held, and easily
23 irritated; reportedly poor sleeper; and refused food
24 not smooth in consistency." That was at twelve
25 months, correct?

1 A Correct.

2 Q And that child was eventually diagnosed with
3 autism, correct?

4 A Yes.

5 Q Now if you go to case two, which is on page
6 sixteen, is there anything at six months that we
7 should know about?

8 A I'll have to read.

9 SPECIAL MASTER HASTINGS: I don't understand
10 the question.

11 MS. CHIN-CAPLAN: I'm asking him to go
12 through some of these case --

13 SPECIAL MASTER HASTINGS: Right.

14 MS. CHIN-CAPLAN: -- and the behaviors that
15 these children demonstrated in comparison to what we
16 saw as shown on the video.

17 SPECIAL MASTER HASTINGS: You're asking him
18 to compare these people to Michelle?

19 MS. CHIN-CAPLAN: Yes.

20 SPECIAL MASTER HASTINGS: All right.

21 BY MS. CHIN-CAPLAN:

22 Q On page 16 of tab --

23 A Do you want me to comment? I don't
24 understand.

25 MR. MATANOSKI: Can I clarify? Do you want

1 him to comment after he reads the case report, or do
2 you want him to go through each of these case reports
3 and then go back through and start again and comment
4 on how it fits in? Because he's finished one, but you
5 haven't asked him to comment on how this seems to have
6 interplay with Michelle Cedillo.

7 BY MS. CHIN-CAPLAN:

8 Q Okay. Why don't we go through each case and
9 then you may comment?

10 A Okay.

11 SPECIAL MASTER HASTINGS: How many cases do
12 we have here?

13 MS. CHIN-CAPLAN: We don't have to go
14 through them all, Special Master.

15 SPECIAL MASTER HASTINGS: Okay.

16 THE WITNESS: So as we discussed before,
17 case one is a male that is three years of age. On the
18 six month assessment, there were some concerns, but
19 very mild, particularly, the orientation to name was
20 inconsistent, depending on the caregivers. There was
21 delay in motor development.

22 But at twelve months, which is six months
23 later, there is more evidence of abnormal development,
24 restricted interested in pleasure in responsiveness to
25 others; brief eye contact; some social smiling, which

1 is reduced and obtained through physical stimulations
2 such as tickling; no social anticipation to peek-a-
3 boo; no anticipatory arm movements; inconsistent
4 orienting to name; and they we carried on -- little
5 reaching for objects; atypical sensory behaviors;
6 atypical motor behaviors; and flapping and finger
7 flicking; marked delay this time in motor development,
8 with general hypertonicity and a few other things.

9 Q Okay.

10 A So if I compare the description of that boy
11 at twelve months of age, there are some overlapping
12 symptoms from what we observed on the first birthday
13 that we deal with this morning. She's clearly
14 hypotonic on that video. She also has postural
15 instability. Eye contact is inconsistent. There is
16 no affection. There are a lot of similarities.

17 Q We'll just go through two more, okay,
18 Doctor? Case number three, also on page 16, please --

19 A Also, so case two, have we done case two?

20 Q Case number three.

21 A Case three, okay.

22 Q Yes, on page 16.

23 A You want me to read six months, twelve
24 months?

25 Q Yes, tell us what the child was like at six

1 months.

2 SPECIAL MASTER HASTINGS: Well, Ms. Chin-
3 Caplan, I'm not one for wanting him to read long
4 passages into the record. I'm still not
5 understanding, and pardon me. It's probably me. Are
6 you asking him to look through these and pick out item
7 that he thinks that each of these children are
8 comparable to Michelle, at the same age? Is that what
9 you want?

10 MS. CHIN-CAPLAN: No, Special Master, I'm
11 asking him to tell the Court the symptoms that these
12 children were exhibiting at this particular period of
13 their lives.

14 SPECIAL MASTER HASTINGS: It's clear in the
15 article. I can read the article.

16 MS. CHIN-CAPLAN: Okay. Then let's proceed
17 on.

18 BY MS. CHIN-CAPLAN:

19 Q So, Doctor, when you look at Michelle's
20 pediatric records, from her pediatrician, as in case
21 number one, was there any indication that she had
22 limited interest or pleasure in responsiveness to
23 others?

24 A Was it mentioned in the pediatric report?

25 Q Right.

1 A No.

2 Q Was there anything mentioned about eye
3 contact and sometimes looking through, rather than
4 seeing, people?

5 A No.

6 Q Was there any description of atypical
7 sensory behaviors, such as interesting carpet
8 patterns, and tracing them with the index fingers?

9 A No.

10 Q Was there any indication of motor behaviors
11 like hand flapping or finger flicking?

12 A No, but are you asking me to comment on
13 that.

14 SPECIAL MASTER HASTINGS: No.

15 THE WITNESS: No, okay.

16 BY MS. CHIN-CAPLAN:

17 Q I'm just asking if there was any indication
18 in the pediatric records that Michelle was exhibiting
19 these symptoms.

20 A And you want a yes or no answer.

21 Q Yes.

22 A Okay. No.

23 Q Was there any indication that she was easily
24 irritated?

25 A No. Actually, yes, she was actually

1 described as fussy I think in the postnatal period,
2 but it's irrelevant.

3 Q Did you say that she was a good baby?

4 A It's mentioned somewhere here.

5 Q She was a good baby. She was a content
6 baby, that she had to be woken up to eat?

7 A Yes.

8 Q So she wasn't easily irritated.

9 A No, there was no mention of that.

10 Q Doctor, was Michelle fussy at all?

11 A I think there was mention of that at one
12 point. But it's not a characteristic which, if it
13 appears, it doesn't happen often. So there is no
14 mention of extreme fussiness or irritability in the
15 pediatric record.

16 Q Did she cling to her mother at all?

17 A How should I know that?

18 Q I'm asking you. Is there any indication in
19 the medical record that she was?

20 A That she was clinging to her mother?

21 Q Yes, clingy.

22 A I don't recall.

23 Q So, Doctor, this article indicates the
24 development of autistic behaviors in children, and
25 they've listed the behaviors that they noted at 12

1 months. You've indicated that her pediatric records
2 don't reflect these symptoms at all. Am I correct?

3 A Yes. I would be happy to affirm more
4 comments on that if you wish.

5 SPECIAL MASTER HASTINGS: No, let her ask
6 the questions, Doctor.

7 THE WITNESS: Okay. Okay.

8 SPECIAL MASTER HASTINGS: You can answer
9 what she ask you.

10 BY MS. CHIN-CAPLAN:

11 Q Now, Doctor, you spoke about the videos that
12 you saw, and you commented on the videos that we saw.

13 A Yes.

14 Q You've also attached an article in support
15 of your opinion, that comments on a retrospective
16 video analysis of children, haven't you? It's
17 contained at Respondent's Exhibit P, Attachment 8.

18 A I don't know where that is. Is this the
19 Baranek study?

20 Q It is the Baranek study.

21 A It's one of the studies. There are many.

22 Q Okay. And, Doctor, did this paper indicate
23 that there were certain early predictors of whether
24 children might go on to develop autism?

25 A Yes.

- 1 Q What were some of those early predictors?
- 2 A Well, I have to read the paper again.
- 3 Q Certainly, take your time, and when you're
- 4 ready, you can let me know.
- 5 A Okay.
- 6 Q I can refer you to page 114.
- 7 A Thank you -- 214, is it?
- 8 Q It's page, I'm sorry, 214.
- 9 A Page 214?
- 10 Q Page 214, yes.
- 11 A Yes, I remember it was like groups of
- 12 behaviors. There were nine, I think, sets of
- 13 behaviors.
- 14 Q Yes.
- 15 A They were quoted on the videotape, which
- 16 included effective expressions, looking, gaze
- 17 aversion, response to name, social touch responses,
- 18 anticipatory posture, motor therapies, object
- 19 therapies, tactile modulation, auxiliary modulation,
- 20 visual modulations, and vestibule modulations, and
- 21 this is also recognized in different ways each time.
- 22 Q Doctor, they compared three different groups
- 23 of children, didn't they?
- 24 A Yes.
- 25 Q There was the autistic group, correct, the

1 developmentally delayed group, and the typical
2 children.

3 A Yes.

4 Q And they saw that these different groups had
5 different rates of activity in certain areas. Is that
6 true?

7 A What do you mean by rates of activities?

8 Q Well, let me refer you to Table Three on
9 page 218.

10 A Yes.

11 Q This table, was this criteria they were
12 looking at to determine whether these children
13 exhibited early signs of autism or not?

14 A Yes.

15 Q Doctor, when you look at this article, does
16 it tell you the most critical criteria in children who
17 would later come on to develop autism?

18 A I think that is based on a discriminant, and
19 that is that they could classify correctly subjects,
20 and their goal was based on 91 percent of their cases,
21 if I am correct. They had nine items in combination,
22 discriminating the three groups with the correct
23 classification rate of 94 percent.

24 Q Okay.

25 A So the combination of all of these

1 indicators allowed them together to ascribe each to
2 the group he belongs to, based just on these
3 indicators.

4 Q So, Doctor, just to be clear, these nine
5 criteria that are listed on Table Three were applied
6 to three different groups of children, and based on
7 the score that they receive, it would be indicative of
8 what was more likely to happen within that
9 developmental group?

10 A Yes.

11 Q It was sort of a prediction of whether a
12 child would be autistic or normal, that type of thing,
13 correct?

14 A Yes, it's a prediction early in the
15 development, based on behaviors observed on the video,
16 to a later diagnosis or lack of diagnosis.

17 Q Doctor, it compared all three groups,
18 correct?

19 A Yes.

20 Q Then it compared the autistic group to the
21 developmental delayed group. Is that true?

22 A Yes.

23 Q The results of that are contained at the
24 bottom of page 219, isn't it?

25 A I have to check.

1 Q The last paragraph beginning with the word
2 "since"?

3 A "Since", yes.

4 Q Does it seem that the most predictive
5 criteria of autism they learned from this test?

6 A Well, they give some class of behaviors,
7 which -- I would have to look at the paper to look at
8 their methodology because it's extracting a paragraph,
9 which doesn't tell me what the analysis is based on.

10 I suspect it's a discriminate analysis, and
11 that they are looking here at a contrast which is only
12 autism against developmentally delayed children.

13 They have looked at nine categories of
14 behavior, and they provide a significant
15 differentiation between autism and developmentally
16 delayed, based on the nine items, of which six, in
17 particular, were contributing to this discrimination.
18 And the six are what is written here.

19 Q What were the six?

20 A Do you want me to read?

21 Q Yes.

22 A Mouthing, in addition to visual stimuli --

23 SPECIAL MASTER HASTINGS: Can you tell me
24 exactly where you're reading from now?

25 MS. CHIN-CAPLAN: We're on Page 220, Special

1 Master.

2 SPECIAL MASTER HASTINGS: Page 220?

3 THE WITNESS: Yes.

4 SPECIAL MASTER HASTINGS: I'm on that page.

5 Where on that page?

6 MS. CHIN-CAPLAN: Directly above the
7 discussion.

8 SPECIAL MASTER HASTINGS: Okay. Go ahead.

9 THE WITNESS: So mouthing, or, in addition
10 to visual stimuli, social-touch aversions, posturing,
11 number of name prompts can affect writing.

12 BY MS. CHIN-CAPLAN:

13 Q Did Michelle demonstrate any mouthing?

14 A Mouthing?

15 Q Yes?

16 A Yes.

17 Q Could you tell the Court what mouthing is?

18 A Yes. There are multiple videos where she
19 actually put toys in her mouth, and that's what she
20 does with multiple toys. We showed a video this
21 morning where she's given a red toy, I think, which
22 she immediately put to her mouth. That's what
23 mouthing is. And she'll also mouthed her fingers in
24 other videos, and she mouthed other toys in several
25 videos. So she's mouthing objects.

1 Q Is that's what's present in the videos that
2 you showed today?

3 A One of them, yes.

4 Q Orientation to visual stimuli?

5 A It depends what they mean by that. It's a
6 label that they gave to a category of behaviors. I
7 have to see what they -- which kind of behavior and
8 writings they used in that category because it could
9 be a different thing.

10 Q It explained on Table 3, which is --

11 A Okay. I'll have to go to it. What it says
12 is occurrences of orientation, stroke attention to
13 nonsocial, novel visual stimuli based on
14 opportunities. It's quite hard to understand what
15 they actually mean there. It's probably very
16 specific, but it's not very obvious to me when I read
17 that. And then it says visual responsiveness, stroke
18 aversion writing. I'm not entirely sure what they
19 mean by that.

20 Q Could that mean whether she's looking at it
21 or whether she's turning away from it?

22 A Yes, but it's a bit unclear.

23 Q Okay. The next one is social touch
24 aversion. What is that?

25 A Well, this probably would be referring to

1 children who have this what we call tight-type
2 defensiveness where they tend to arch back when they
3 are taken so that's a kind of certain period which you
4 see some children exhibit but not all.

5 So if I look at the category on Table 3, it
6 says social touch aversions. Yes. It's occurrences
7 of social touch aversion based on opportunities for
8 physical contact.

9 Q So essentially what you just said.

10 A Yes.

11 Q She's arching away from the person. You're
12 turning away when somebody is trying to talk to you,
13 that type of thing?

14 A Yes, but probably when you write video
15 tapes, you go into much more details to specify which
16 kind of behavior you actually write in that category.
17 That is a global description which doesn't really
18 give us a lot of details about what they observed.

19 So when they do video coding, it's much more
20 specific. Because if you have a child who arches
21 back, there is a point where if it's just a movement
22 like that, you will not go there, so that particular
23 operation on the definitions which are laid out in
24 procedures and manuals. It's a more complex than it
25 appears in Table 3, but that's the concept behind it.

1 Q Did you see, in the videos that you
2 presented to us, any social-touch aversion by
3 Michelle?

4 A No.

5 Q Then it says posturing. What is posturing?

6 A Posturing, the way you stand and you hold
7 your body in various situations. If you stand on your
8 feet, or if you sit, so it's the degree of balancing,
9 righting the position, and balance that the child has.

10 Q Balance with your hands, is that what you
11 just said?

12 A No, balance -- the overall balance that the
13 child maintains.

14 Q Doesn't posturing mean abnormal placement of
15 your arms, of your limbs?

16 A Usually -- no, it depends in which context.
17 Sometimes with the expression is: use of hand
18 posturing. When the hand is held in a particular way,
19 it will be an abnormal hand posture. But it can be
20 used in different ways as well, so I'd have to see
21 what they included in that category.

22 Q I think you have already commented on the
23 number of name prompts on the video, correct?

24 A Did I comment?

25 Q Yes?

1 A Yes, they have a category which is a number
2 of name prompts, yes.

3 Q The last category they mentioned was: affect
4 leading.

5 A Yes.

6 Q What is affect?

7 A Again, I have to check with the -- what did
8 they include in this category, so I'm looking back on
9 Table 3.

10 The number of name prompts is explained.

11 Physically, it's a response to name, and it's a
12 proportion of the time the child responds to name,
13 based on opportunities.

14 so number of prompts given by the adult.

15 It's the proportion of interactions where the child is
16 called and orients to his name.

17 Q Okay. How they react to people in general,
18 is that it?

19 A No, it's more specific. It's when the name
20 is called, does the child orient? And you have to --
21 when you write a video, for instance, you try to
22 insure that the orientation must be seen behaviorally.

23 Because if you have the child who is
24 actually looking at you, and you call his name, or her
25 name, it's very hard to see if there is actually a

1 behavioral response, or orientation, because the child
2 is already looking in the same visual field.

3 Often we would not count that as a relevant
4 behaviors. We would like to look at situations where,
5 for instance -- our assessments, we have in the ethos,
6 we use that press to see if the child oriented to him.
7 We are careful when we do that to not be in front of
8 the child, or not be in his visual field.

9 If the child is playing in the room and
10 doing these things, we stand behind him or sideways,
11 so that when we call his name, then to see that if he
12 reorients, there should be a clear orientation towards
13 the examiner.

14 These are the precise ways to do it
15 clinically. And there are, of course, I'm sure much
16 more precise ways to record that on tapes.

17 Q So the affect reading is not the same thing
18 as affective expressions?

19 A I don't know.

20 Q That would be on the table, again on Page
21 218.

22 A They call that affect writing on 220. In
23 Table 3, it seems to be affective expressions. I
24 suppose it's the same category. I don't know.

25 They use different terms. The affective

1 expressions in Table 3 means frequencies of positive
2 and negative expressions. Because in these roles, the
3 qualitative writing of range and intensity of
4 affective expressions, so it's displayed. They use a
5 different terminology later, which they call: affect
6 writing.

7 Q Thank you. So, Doctor, when we to go on to
8 Page 221 of this article, right under the table, the
9 very last sentence in the first paragraph, doesn't it
10 say: it appears premature, however, to use these items
11 as a screening tool until they can cross-validated in
12 future retrospective, as well as prospective studies.

13 That's what it says, correct?

14 A Uh-huh.

15 Q So they're cautioning you to use these types
16 of tools, aren't they, because they don't know the
17 validity of them yet, correct?

18 A No. I think you don't read the way they say
19 yes. They are talking here about extrapolating the
20 results of their work into a context where they would
21 be screening it in a different context: population
22 screening of young children with autism.

23 That is not something that they advise to do
24 at this stage. It doesn't mean that their results are
25 invalid. In fact, what you just made me review is

1 that the comparison, or the contrast, between children
2 with autism and children with developmental disorders,
3 they can achieve a nice separation on six of the
4 categories of behaviors between these two groups. So
5 they could do it in their study based on video
6 analysis.

7 Now, in the discussion, the goal of that is
8 to try to identify early manifestations of the autism
9 phenotype, not for to talk about it, just to apply
10 that to screening, or early detection efforts in
11 context where you would have much more quick screening
12 in instruments, or testing done by people who don't
13 have necessarily professional expertise in autism.

14 So before you move towards applying these
15 results to a screening approach at a population level,
16 you need to be cautious and you need more data to
17 insure that you're correct.

18 But it doesn't invalidate what they found,
19 which is that they could discriminate between children
20 with autism and children without autism but
21 developmental delays. The behaviors which
22 differentiate the two groups are, as we said,
23 affective expression, response to name, and also the
24 behaviors that we have seen this morning.

25 Q The take-away message is really: Use with

1 caution, isn't it?

2 A Yes, of course. The screening is not done
3 by people like me understand. I am an expert and I
4 see hundreds of kid who I can make a professional
5 opinion, or a diagnosis in a situation that would be
6 applicable to the common general practitioners,
7 pediatricians, or nurses. So the screening is in a
8 very different context.

9 Q Okay. Doctor, you've written a number of
10 articles, as we've discussed earlier today, correct?

11 A Uh-huh.

12 Q Quite a few of them are epidemiological
13 studies, correct? And there a few that aren't,
14 though, or they have a different type of topic, isn't
15 that true?

16 A Yes.

17 Q Doctor, you did write an article: MMR in
18 Autistic Enterocolitis. That's Respondent's Exhibit
19 P, reference 64. Do you recall this article?

20 A Yes, it's a commentary that I was asked to
21 write for Molecular Psychiatry following the
22 publications of the Wakefield group and --

23 Q Okay. Doctor, I'm just going to ask you,
24 what is your conclusion in this article?

25 A Well, I dealt mostly with the epidemiology

1 and concluded that, up to that point, in 2003, that
2 there had been a consistent failure to support the
3 hypothesis of Wakefield in terms of an increasing risk
4 of autism following MMR immunizations, or in terms of
5 identifying an autistic enterocolitis phenotype, which
6 would have its own validity.

7 Q Doctor, when you compared in this article,
8 did you come to the conclusion that there's no such
9 thing as autistic enterocolitis?

10 A Yes, I said there was no evidence for a new
11 phenotype of MMR-triggered autism with associated
12 enterocolitis, yes.

13 Q Do you believe that autistic children do not
14 have bowel problems?

15 A Actually, I have no beliefs in general. I'm
16 a scientist. What I look at is the evidence, which I
17 generate myself in studies, or when I review studies
18 of others. So I have no particular set of beliefs
19 which drive my opinion.

20 Q When you say you have no belief, does that
21 mean that you have no opinion?

22 A No, I have opinions. I don't believe things
23 just for the sake of believing them.

24 Q Okay. So your opinions is that you don't
25 believe they have bowel problems, is that it?

1 A No, I think this is a question which needs
2 empirical data to address that. What is your question
3 exactly, bowel problems?

4 Q Yes, that's what I asked you. So your
5 opinion right now is you need more data?

6 A About what, exactly. Could you --

7 Q As to whether autistic children have bowel
8 symptoms?

9 A Bowel symptoms, as opposed to bowel
10 disorders?

11 Q Bowel symptoms, first?

12 A Okay. I think it is still unclear.
13 Clearly, you have several reports which are based on
14 clinical samples, which have often been referred to:
15 part are clinical, part are gastroenterology clinics.
16 And that is part of the problem of the
17 children in the insure case series of Dr. Wakefield's:
18 That, of course, they have GI symptoms because in
19 order to be seen by him, they had to be having GI
20 symptoms. That doesn't really address the questions
21 in our reports, which have been deriving from clinical
22 centers where the gastroenterologists look at that are
23 not informative on this question. For that, we need
24 to have epidemiological data on representative samples
25 of children with autism.

1 It's not always easy to obtain, but that's
2 what we would need to assess whether or not they have
3 bowel symptoms of different kinds.

4 In addition to that, besides obtaining a
5 representative series of cases of autism, the question
6 is: Compared to what? So you need to think about
7 which kind of control group is necessary in such
8 studies. And, in addition to comparing the rates of
9 bowel symptoms in autism to these symptoms in
10 typically developing children, it will be also very
11 useful to have the same data on children who have non-
12 autistic other kinds of developmental abnormalities.

13 This kind of data I've been, up to now, I
14 think largely missing and the MMR Review, which was
15 published in 2002, I think, precisely pointed out to
16 this problem that there are no good epidemiological
17 data on this issue and there needs to be a few of
18 these, but not so many.

19 Q So this article here is your article,
20 correct?

21 A Yes.

22 Q Is this an epidemiological study?

23 A This is not a study. This is a commentary.

24 Q So the topic is: MMR an Autistic
25 Enterocolitis, consistent epidemiological failure to

1 find an association. It's a review, is that what
2 you're telling me, of the literature out there?

3 A You could say that it's a commentary which
4 was invited by the editor of the journal just to
5 quickly -- it's based on a review of existing data, at
6 the time about this question, yes.

7 Q Okay. You say it's a commentary. Do you
8 have any conclusions in your commentary?

9 A I don't recall what I said. Yes.

10 Q What is your conclusion?

11 A Where do you want me to start?

12 Q Wherever you would like.

13 A Well, let me see. In that paper, what might
14 be interesting and relevant to our discussions. I
15 reviewed some studies which addressed the question of:
16 Is there an increased risk of autism following MMR
17 immunizations, in various countries.

18 We had, at that time, data from, in
19 particular the UK, which showed that there was no such
20 evidence. I'm referred in particular to the studies
21 by Brent Tanner, which looked at case series at that
22 time of children studied between 1979, as I recall, up
23 to 1991, a large sample size of almost of 500
24 children.

25 They were tested in various ways whether or

1 not the introduction of MMR in the UK on a large scale
2 in 1988 was associated with an increase in the rates
3 of autism. And using a various approach, they said
4 that they failed to find any such association, so
5 that's one study.

6 There was another study by DeWilde et al.,
7 which was interesting in the sense that they followed
8 up on the assumption by Dr. Wakefield that if the
9 onset of autism was immediately after MMR, as he has
10 posited in his original paper. He actually said: 6.3
11 days after the MMR vaccination on average, there would
12 be a profound regression, loss of sill and GI symptoms
13 occurring de novo in a child who was otherwise
14 developing normally up to that point.

15 Obviously, that should worry parents, and we
16 should see parents going to consult their GPs in the
17 weeks following this change in their child. The UK
18 has a multiple existing database, which can be used to
19 test hypothesis of that kind and to use one of the
20 existing general practitioner's electronic database.

21 They looked at, I think, controlled children
22 and children who were later diagnosed at the age of
23 three or four. On all of these children, they had
24 information about MMR exposure, whether or not they
25 received the vaccination and the date.

1 So what they did is they created an interval
2 for children who were either normal children
3 throughout or later diagnosed with autism. They
4 looked at the MMR date, and they looked at how often
5 following the MMR immunizations parents of these
6 children started to consult their GPs. And the
7 prediction is that if indeed there is a massive change
8 or regression, something new occurring, you should
9 expect to see parents consulting their doctors in the
10 weeks or a few months following this change.

11 So, in the sixth month after the MMR
12 immunizations, they looked at rates of activity or
13 consultations by parents with their GPs. They found
14 no difference, suggesting that there was no particular
15 increased frequency of consultation with doctors
16 following the MMR immunizations.

17 They found that just before the diagnosis
18 was made, at three or four years of age in children
19 who ultimately were diagnosed in the six months which
20 preceded the diagnosis, then there was increased
21 consultation by the families, suggesting that the
22 database was sensitive enough to capture health
23 services contacts which were meaningful, by the
24 parents of these children.

25 Q Those two studies that you mentioned, they

1 were looking at whether MMR could cause autism, wasn't
2 that it?

3 A The first one, yes. The second one is more
4 -- yes. It's testing the hypothesis. It's more
5 testing the idea that there is a regression following
6 MMR in otherwise previously normal children.

7 Q My question to you was, do you believe
8 autistic children have bowel symptoms?

9 A Again, I have no beliefs on that. I'm
10 looking at the evidence.

11 Q Well, Doctor, what is the conclusion of this
12 commentary on MMR in Autistic Enterocolitis,
13 Consistent Epidemiological Failure to Find an
14 Association. What are you referring to here?

15 A Let me go a couple of sentences before.

16 SPECIAL MASTER HASTINGS: Ms. Chin-Caplan,
17 I'm not sure what you're trying to ask, what you're
18 asking. Your asking him to summarize the conclusion
19 of the commentary?

20 MS. CHIN-CAPLAN: Correct.

21 SPECIAL MASTER HASTINGS: The point of the
22 commentary?

23 MS. CHIN-CAPLAN: Yes.

24 SPECIAL MASTER HASTINGS: Dr. Fombonne, does
25 that help?

1 THE WITNESS: I'm not sure exactly what's
2 the question. Yes, but I can summarize the
3 conclusions at the time of this commentary, which is
4 to say: So far, in 2003, when we looked at studies of
5 an epidemiological nature, and design, which have
6 looked at the hypothesis of Wakefield, that implies
7 different designs, different set of hypothesis.

8 There was no sample for this association, so
9 that's what is the main conclusion of the paper.

10 Also, the paper points at flaws in Dr.
11 Wakefield's research. For instance, something that
12 has never been addressed by him in subsequent studies
13 whereby -- identified that when one of these sample, I
14 think the 2000 sample, included not only children with
15 autism but also children with ADHD, and children with
16 dyslexia, and children with schizophrenia. Because
17 that's what they did in one of these studies.

18 They are inspecting the elements because
19 there are also children who were not autistic in the
20 same sample which is analyzed in various papers. This
21 is something that is written in this commentary, and
22 this is a serious flaw in his original results which
23 have not been addressed by him since then.

24 But, otherwise, looking at the other
25 epidemiological efforts at that time, there was no

1 support by research from others, including mine, to
2 argue for the existence of a new phenotype of autism,
3 which would be MMR induced associated with
4 enterocolitis or GI symptoms, or GI disorder.

5 And there was no evidence that there was an
6 increased risk of autism in populations where MMR was
7 introduced, or an increased risk in children who where
8 individually exposed to MMR.

9 BY MS. CHIN-CAPLAN:

10 Q My question to you, though, Doctor, is, what
11 study are you relying upon when you say that there is
12 no relationship between MMR and autistic
13 enterocolitis?

14 A On the studies which are referenced in the
15 commentary.

16 Q Do those two studies specifically look at a
17 child with bowel disease?

18 A You ask me about bowel disease now?

19 Q Yes, bowel disease. Let's start with bowel
20 symptoms. Does either one of these studies look at
21 children with bowel symptoms who happen to be
22 autistic?

23 A Yes.

24 Q Which one?

25 A It's referenced in No. 11, referenced in No.

1 14, referenced No. 15.

2 Q No. 15.

3 A Referenced in No. 16.

4 Q There is just a citation, Black Sea at
5 *British Medical Journal*, is that it? Is that what
6 you're referring to?

7 A Yes.

8 Q Is there a difference between bowel symptoms
9 and bowel disease in your mind?

10 A Yes.

11 Q What's the difference?

12 A One is symptom, the other is disorder. It's
13 very different.

14 Q Do you have an opinion on whether these
15 children have a bowel disorder?

16 A Yes.

17 Q What is your opinion?

18 A My opinion is based on studies again. At
19 lease in that reference, you can see the reference 16,
20 which is my paper in *The Lancet* in 1998. You can see
21 it referenced in 15, which is Black in 2002.

22 Let me explain these studies because you are
23 asking about them. When Dr. Wakefield published his
24 results, I was in the UK and there was an NRC review
25 of his research, which includes rules.

1 And I was involved with many others to
2 review it, his findings. At that time, because I was
3 interested in looking at empirical evidence in support
4 of his ideas, or to refute his ideas, I had already
5 actually conducted some research on this particular
6 issue.

7 The research I did was to look at the
8 incidents of inflammatory bowel disorders, including
9 Crohn's disease, a sort of colitis, and other kinds of
10 IBDs in two large samples of British children who were
11 referred at the Maudsley Hospital at which we had a
12 huge database, which collected data on psychiatric
13 diagnosis, but also medical conditions.

14 We had, as I recall, about 750 children with
15 a PDDI diagnosis and about 8,000 psychiatric controls
16 with other diagnoses than autism. In these children,
17 we had data about Crohn's disease and also
18 enterocolitis.

19 And there was another sample. It was a
20 French epidemiological sample, which comprised I think
21 174 maybe children with PDDIs, and a control group of
22 over 5,000 children, epidemiologically defined who had
23 different types of handicaps of psychiatric diagnosis
24 than autism.

25 Again, we had on these children information

1 about their medical history, and whether or not they
2 had inflammatory bowel disorders. In both samples,
3 there was no case of autism in the British studies, in
4 the French studies, with any of this inflammatory
5 bowel disorders.

6 There were a few cases in the controls
7 suggesting that were reported in the two samples, but
8 there was no association clearly in that study between
9 autism and inflammatory bowel disorders.

10 This was presented as a preview to Dr.
11 Wakefield. I had done that study because it was to
12 follow-up what I knew about his previous research,
13 which was mentioned this morning. Before he moved
14 onto the autism MMR question, he had done about ten
15 years of research which was published here and there,
16 where he was claiming that the measles virus was
17 responsible for an epidemic of Crohn's disease in
18 adult populations, and that created some concern.

19 There was a string of research studies done
20 by others who never replicated his findings. And
21 then, he moved onto autism later, and it's a fight
22 which has been forgotten by many that he had done so.

23 My hypothesis was because he posited that
24 the measles virus was leading to Crohn's disease, and
25 was leading now to autism, I said: If he's right, we

1 should see an increased incidence of inflammatory
2 bowel disorders in children with autism, based on his
3 theories. And that was not supported at a very early
4 stage.

5 It has been since then replicated. You
6 could see the Black study, which is in reference No.
7 15, in the *British Medical Journal*, is based on a
8 large general practice where there is data with GPRD.
9 They published that in the BMJ. It's again testing
10 this particular hypothesis and showing no increased
11 incidence of IVD in children with autism compared to
12 controls.

13 So, there are now two studies showing no
14 increased incidence of IVD in children with autism.
15 There is also a study published I think last year by
16 Richler et al. based on a large sample of the CDC work
17 in the U.S. based on investigators in autism research
18 where they looked at regressive autism versus
19 nonregressive autism.

20 They provided results about the incidence of
21 IVD in regressive versus nonregressive autism and
22 showed that there was no difference. So not only
23 there is no increased risk in autism in general, but
24 there is also no increased risk in children with a
25 sub-type of regressive autism.

1 So my opinion based on the evidence which I
2 reviewed then and has not changed is that there is no
3 association and that autism does not increase the risk
4 of inflammatory bowel disorders in children. So I
5 think there is no association between the two.

6 Q Okay. You said at Black in support of what
7 you just stated, and you mentioned a French
8 epidemiological study, is that true?

9 A No, the reference 16 --

10 Q Sixteen?

11 A -- is my own study. But research in The
12 Lancet shortly after the Wakefield paper, which
13 received much less attention, I must say. But it's
14 based on large sample with control groups. So it has
15 some validity.

16 Q It's 15 and 16, is that what you're saying?

17 A Yes.

18 Q Now, Doctor, you were here in the courtroom
19 last week, correct?

20 A Fair enough.

21 Q Did you say that you are a member of Autism
22 Speaks?

23 A No, I didn't say I was a member of Autism
24 Speaks.

25 Q Are you associated with Autism Speaks in any

1 capacity?

2 A It depends by what you mean by associated
3 with them. So do you want me to expand?

4 Q Do you have a role in the organization at
5 all?

6 A No, they invited me to part of the review
7 board to review the grants that they allocate.

8 Actually, I could not do in two years in a
9 row, but I did that three years ago. I was part of
10 the scientific review committee for the location of
11 funds for research in mostly, it's not just North
12 America. It's world wide. That's an activity I did
13 for them.

14 The other connection I have with them, and I
15 don't know if it's an association, is: They fund some
16 of my research. The training grant that was mentioned
17 before, which is this six-year attempt to boost
18 research capacity in autism in Canada, which involves
19 several universities, summer school.

20 The funding is a mixed funding coming from
21 CIHR, which is the equivalent of NIH in Canada. But
22 Autism Speaks, or more exactly NAR, which was a
23 previous organization which is now Autism Speaks, has
24 contributed to that grant.

25 Then I am -- you know, they invited me to

1 various -- they have been influential with the CDC and
2 other people at NIH to develop a network of
3 investigators, which are interested in the emerging of
4 autism, or conducting research on the emerging of
5 autism either in the U.S. and to try to promote a
6 worldwide efforts to study autism with an
7 epidemiological perspective.

8 There is this network which is informal that
9 they have. So I was invited to brain storm on the
10 creation of this network. Then there as a couple of
11 meetings, so I had discussions with them about that.
12 And a few other things, if you --

13 Q You heard in Court last week, though, that
14 Autism Speaks hosted a gastroenterological workshop in
15 Boston, correct?

16 A Yes, I went, yes.

17 Q Doctor, didn't Autism Speaks indicate that
18 autistic children's GI problems deserved to be worked
19 up?

20 A I do not know what they indicated. I didn't
21 see the papers, but I can assume that it said that.
22 That's okay.

23 Q I'm going to refer the Court to Petitioner's
24 Trial Exhibit No. 5. Could you just kindly read that
25 into the record, Doctor?

1 A Where do you want me to read? Here?

2 Q Yes.

3 SPECIAL MASTER HASTINGS: Not the whole
4 thing.

5 MS. CHIN-CAPLAN: No.

6 SPECIAL MASTER HASTINGS: What are you
7 asking him to read?

8 MS. CHIN-CAPLAN: Just the two paragraphs.

9 SPECIAL MASTER HASTINGS: Okay.

10 THE WITNESS: Responding to community
11 interest, Autism Speaks hosted a workshop on autism
12 and gastroenterology in Boston on October 13, 2006.

13 The objectives of the workshop were to
14 review current scientific evidence for GI issues
15 associated with autism, to divvy up consensus
16 scientific priorities for autism gastroenterology
17 research, and to suggest an approach to establish best
18 clinical practices for autism and gastroenterology.

19 You want the next paragraph?

20 MS. CHIN-CAPLAN: Please.

21 THE WITNESS: In an effort to capture all
22 perspectives on this topic, the participants included
23 members of Autism Speaks Scientific Affairs Committee,
24 and leading experts on pediatric gastroenterology and
25 autism.

1 The discussion was comprehensive and
2 productive. Please watch this space for a synopsis of
3 the consensus recommendation.

4 BY MS. CHIN-CAPLAN:

5 Q Thank you, Doctor. So from what you read,
6 Doctor, would it be fair to state that Autism Speaks
7 believes that autistic children have gastroenterology
8 problems?

9 A No, I would not endorse what you just said.
10 Autism Speaks is an organization, which has an
11 agenda, which is very different than the agenda of
12 scientific institutions or academies. So, they pursue
13 scientific activities, but they, also, are sensitive
14 to needs or partials of a different nature. So, what
15 they say doesn't mean that it's entirely driven by the
16 needs of scientific agenda. I would say that first.

17 Secondly, I don't know exactly who in Autism
18 Speaks involved in that, so I cannot say. Autism
19 Speaks is a large organization with different
20 tendencies, different people. So I wouldn't say
21 Autism Speaks is an organization that endorses that
22 necessarily.

23 But, if your question is to say, and if you
24 want my opinion on that, is to say, is it important to
25 investigate that. Yes, certainly. And there are

1 multiple aspects of the management of autistic
2 children, which need to be improved. That includes GI
3 symptoms, if they have more than usual, also, sleep
4 disorders, behavioral problems. And various
5 institutions are doing that. But, that has to do with
6 the clinical care and the management of a complex
7 problem. It has nothing to do with the fact that GI
8 symptoms are causally related in some sort of pathways
9 to the disease or the disorder. So, I think it's
10 important to separate the issues. One has to do with
11 management concerns that the families need to access
12 in order to better medical care, which is obvious, and
13 that's fine, and a question, which has to do with an
14 assertion between autism and related medical
15 conditions, both.

16 Q Doctor, you've written another article,
17 which is contained under Respondent's Exhibit P, Tab
18 42. Doctor, the title of this article is 'No evidence
19 of persistent measles virus and peripheral blood
20 mononucleus in children with autism spectrum
21 disorder,' is that correct?

22 A Yes.

23 Q And you are the second author on this
24 article?

25 A I can tell you why?

1 Q Pardon me?

2 A I can tell you why I'm the second author,
3 because that article is mostly the work of the McGill
4 Laboratory of Dr. Brian Ward, who will speak later
5 this week. And all questions, which have to do with
6 PCR or the virology should be directed to him.

7 Q Okay. So what was your contribution to this
8 paper?

9 A Well, we had the idea, Dr. Ward and myself.
10 We met when I came to Canada. I met with him vis-à-
11 vis the MMR issue, because I was coming from the U.K.
12 and still involved in various things. And I was
13 actually looking at the profound and durable effect of
14 this controversy on rates of vaccination. And in
15 2002, the uptake of MMR vaccination in the U.K. had
16 dropped from 95 or 96 percent, the level at which they
17 were before the litigation, to a low of about 82
18 percent on average, which meant that her immunity was
19 not guaranteed anymore.

20 And as we said before, outbreaks of measles
21 were appearing. There were a medley of epidemics to
22 come. Children died in Ireland, and parents came to
23 be very worried. Parents of autistic children were
24 worried, asking questions. So some research needed to
25 be continued even though the evidence was already

1 quite solid to refute this association.

2 So, as we met there, I was developing a
3 service for autistic children which didn't develop for
4 substantial reasons the last five years. I was
5 thinking of ways to use our clinical activities to ask
6 such questions. And what I did is I actually
7 submitted a grant in which we would look at various
8 aspects of the biology of autistic children. We
9 looked at their immune system. We looked at heavy
10 metals, including mercury, but not only mercury. And
11 we looked at the MMR issuing that grant.

12 So it was a grant basically saying we assess
13 young children. We often take blood samples from
14 them, so it's not a big deal to take a bit more blood
15 and address these questions by doing further research.
16 So that was how it developed. And in that -- well,
17 that's it. I speak too much.

18 Q So, you gave him the idea, is that it?

19 A No, no, no, no, no. No, I didn't give him
20 the idea. He's not a man where you really need to
21 give ideas. He has his own ideas and I had my own
22 ideas and we just met and decided it would be possible
23 to do that and that's what we did.

24 Q So my question to you is what input did you
25 have in this article?

1 A Oh. I did -- well, first, we conceived --
2 we designed the study together. And there was an
3 aspect of the selection of patients, which is
4 extremely important here. And all the patients in
5 this study had been assessed by myself. They were
6 characterized. They all had had ADIs, ADOSs, and that
7 was my main contribution, in terms of the data
8 collection on this one. My second contribution was
9 the funding and the initial discussion and the design
10 of the study was by all. All the lab work was his.
11 And then I was, of course, involved in the writing up,
12 especially in the part, where I can have ideas or
13 comments.

14 Q Okay. So, Doctor, there is a statement
15 underneath here, 'financial disclosure in the United
16 States.' Do you have it in front of you?

17 A Yes. Where is it? It's on the first --

18 Q It's on the first page.

19 A The copy is not clear, so maybe you --

20 Q Actually, it's 'financial disclosure in the
21 United Kingdom.' I think I said 'the United States.'

22 A Yes.

23 Q Are you there?

24 A Yes, I'm here.

25 Q Okay.

1 A It's the --

2 SPECIAL MASTER HASTINGS: Why don't you read
3 it to him?

4 THE WITNESS: My copy is not good, so I
5 can't read it.

6 BY MS. CHIN-CAPLAN:

7 Q So, Doctor, just follow along with me.

8 A Yes.

9 Q 'Dr. Fombonne has provided advice on the
10 epidemiology and clinical aspects of autism to
11 scientists and advising paths, to MMR vaccine
12 manufacturers for fee and to several government
13 communities between 1998 and 2001.' Have I read that
14 correctly, Doctor?

15 A Yes.

16 SPECIAL MASTER HASTINGS: Actually, you said
17 'communities,' rather than 'committees.'

18 MS. CHIN-CAPLAN: Oh.

19 SPECIAL MASTER HASTINGS: But, go ahead.

20 MS. CHIN-CAPLAN: Okay.

21 BY MS. CHIN-CAPLAN:

22 Q Doctor, if you would skip down to the
23 beginning of the third sentence. It says, 'since June
24 2004, Dr. Fombonne has been an expert witness for
25 vaccine manufacturers in the U.S. thimerosal

1 litigation.' Have I read that correctly?

2 A Yes.

3 Q Doctor, with respect to your work in the
4 U.K., can you just tell us when you started working in
5 the U.K. on the MMR litigation?

6 A When did I started to work on --

7 Q When did you start?

8 A -- on the litigation?

9 Q In the MMR litigation in the U.K.

10 A I was not really involved in the litigation
11 in the U.K. As is mentioned here, when we discussed
12 this morning that this advisory committee with the
13 chief medical officer, it had nothing to do with the
14 litigation. It was just to give him some basic
15 scientific facts and advise him on the science. It
16 has nothing to do with the litigation. So, the only
17 contact I had with the litigation in the U.K. was to
18 consult twice with a vaccine manufacturer. They asked
19 me, can we meet with you to discuss about autism, the
20 epidemiology, what do you know. So, that was one
21 meeting. And then there was a second meeting, where
22 they asked me similar questions and they asked me to
23 review the notes of a child, the medical notes of a
24 child, to get my opinion. So, that's what I did. I
25 made it clear to them initially that I didn't want to

1 be part of the U.K. litigation. So, that's -- and
2 that's what I say, I sent them a letter and that was
3 it. I was not involved further in the U.K.
4 litigation.

5 Q And when was that?

6 A It was -- I would say probably my first
7 contact with them was fall 2000, I would think, and
8 the second one was spring 2001, because then I moved
9 to Canada.

10 Q Okay. And, Doctor, it indicates here that
11 since 2004, you've been consulting to drug
12 manufacturers in the United States on thimerosal
13 litigation.

14 A Yes.

15 Q Is that correct?

16 A Yes.

17 Q Now, Doctor, this is the first time I've
18 seen this type of financial disclosure in your pot.
19 Have you disclosed this previously?

20 A I don't know.

21 Q Well, let's take a look at your publications
22 that you cited here.

23 A Which one?

24 Q Let's start with Respondent's Exhibit P,
25 page --

1 SPECIAL MASTER HASTINGS: Do you have a tab
2 number?

3 MS. CHIN-CAPLAN: I am looking for it,
4 Special Master.

5 SPECIAL MASTER HASTINGS: Okay.

6 BY MS. CHIN-CAPLAN:

7 Q Let's start with Tab 67. You indicate that
8 you began working 2004 for vaccine manufacturers in
9 the United States. This was accepted in March 2004.
10 Did your involvement predate this?

11 A Sorry, which involvement?

12 Q Did your involvement with the drug
13 manufacturers predate the article publication date
14 here?

15 A You mean in the U.K. or in the U.S.?

16 Q I mean here. But, you said the U.S., didn't
17 you, for the last one?

18 A Yes, in the U.S.

19 Q Right.

20 A This was done before.

21 Q Okay.

22 A I mean, I think so. It was published in
23 March 2004.

24 Q Okay. And do you recall when you began
25 working with the drug manufacturers here in the United

1 States?

2 A Oh, you just read it. It's June 2004.

3 Q June 2004. And this was published in March
4 of 2004 --

5 A Yes.

6 Q -- correct? Okay. What about the next
7 article? That would be Tab 68. This article was
8 published in 2005.

9 SPECIAL MASTER HASTINGS: Before we leave
10 this, I didn't understand -- maybe you can help me,
11 Doctor. You said, you just read it, when she was
12 asking about when you began with the government
13 manufacturer. Was that in the previous -- I'm
14 confused about what you meant by that, 'you just read
15 it.'

16 THE WITNESS: I'm sorry, she -- counsel just
17 read the financial disclosure --

18 SPECIAL MASTER HASTINGS: From the previous
19 article.

20 THE WITNESS: The article.

21 SPECIAL MASTER HASTINGS: Okay. That's what
22 you were referring to?

23 THE WITNESS: Yes.

24 SPECIAL MASTER HASTINGS: Okay.

25 THE WITNESS: And there is a sentence, which

1 says, 'since June 2004.'

2 SPECIAL MASTER HASTINGS: Okay. Thank you.

3 Thank you. Sorry. Go ahead, Ms. Chin-Caplan.

4 MS. CHIN-CAPLAN: Thank you, Special Master.

5 BY MS. CHIN-CAPLAN:

6 Q So, Doctor, on Respondent's Exhibit P, Tab
7 68, the title of this is 'the changing epidemiology of
8 autism.' It was published in 2005. Is there a
9 financial disclosure in this article?

10 A Yes.

11 SPECIAL MASTER HASTINGS: Your answer was
12 yes?

13 THE WITNESS: Yes.

14 BY MS. CHIN-CAPLAN:

15 Q Where is it?

16 A It's in the article at the end.

17 Q Can you show me? I couldn't find it.

18 SPECIAL MASTER HASTINGS: At the end, did
19 you say?

20 THE WITNESS: Yes, at the end, page 292.

21 SPECIAL MASTER HASTINGS: All right.

22 BY MS. CHIN-CAPLAN:

23 Q Okay. 'Dr. Fombonne is an expert witness
24 for vaccine manufacturers in the financial
25 litigation.' And did you do the same for Tab 69?

1 A It doesn't seem to appear here. If it does
2 not appear, it's by choice of the editor, not by me.

3 Q Okay. Because I didn't see one.

4 A Uh?

5 Q I did not see one.

6 A No, no, no, no. It was something about --
7 they sent a form and everything was determined that
8 parties selected to put something. I think their
9 concern -- because this was organized by -- yes, this
10 was organized by -- it was an educational grant by the
11 drug industry in fact. It was a whole issue about
12 autism and there were also like lectures done on the
13 web to educate doctors.

14 And I think their main concern was to what
15 is appearing at the end of the article, which is
16 disclosure of -- so I think they were concerned about
17 links of funding that drug study. But my disclosure
18 would have been forwarded to them.

19 Q I'm sorry, I missed that.

20 A My disclosure would have been forwarded to
21 them, most of them.

22 Q And it's not included here?

23 A No, but it's not by choice, is what I said.

24 Q The next three articles, Doctor, they appear
25 to be book chapters, am I correct?

1 A I don't know.

2 SPECIAL MASTER HASTINGS: Can you repeat?

3 BY MS. CHIN-CAPLAN:

4 Q Sure, Tab 70, 71, and 72, they appear be
5 book chapters, is that correct?

6 A Yes, yes.

7 Q Okay. You don't normally disclose things
8 like that in a book chapter, do you?

9 A No. It's neither requested or required.
10 It's not something that you do, not that I know of.

11 Q And I see under Tab 74, it states, 'since
12 June 2004, Dr. Fombonne has been an expert witness for
13 vaccine manufacturers in U.S. thimerosal litigation.
14 None of his research has ever been funded by the
15 industry.' Is that what it says?

16 A That is correct.

17 Q That seems to be it, the articles that you
18 cited, am I correct?

19 A Yes.

20 Q So, Doctor, have you testified for drug
21 manufacturers in the United States?

22 A Yes, once.

23 Q One? Could you just generally describe to
24 the Court where it was?

25 A It was what is called a Daubert hearing in a

1 court in Texas.

2 Q And how much did they pay you to testify?

3 A What do you mean

4 Q For the Daubert hearing?

5 A To testify?

6 Q Yes.

7 A I'm paid by the time I spend reviewing the
8 records, writing affidavits, being deposed, or
9 testifying in court. So, it's based on an hourly
10 rate.

11 Q And what is your hourly rate?

12 A It's \$500 an hour.

13 Q And, Doctor, you said it was a Daubert
14 hearing. Did the case end, at that point?

15 A Yes.

16 Q And how much in total were you paid for that
17 Daubert hearing?

18 A The case, you mean?

19 Q Yes.

20 A I don't keep track of that. You want a
21 figure? I don't know. I started on this work in June
22 2004 and I think the hearing was in, I think, February
23 or March 2005. So, there was about eight or ten
24 months of work. And I would guess, I have no clear --
25 I would guess probably \$70,000 or \$80,000 in total for

1 that court.

2 Q And are you currently working on any other
3 cases for the drug manufacturers?

4 A I am, very -- yes. Occasionally, I've been
5 involved in reviewing some medical notes of, I think,
6 a couple of cases, on which I have no -- I didn't have
7 to produce evidence, because the cases were dismissed
8 by the court in the process or suspended. It seems to
9 be very long and changing all the time. And there was
10 another case, which is active, which I am involved in,
11 but I have not submitted any report yet.

12 Q So, there is one active case currently
13 pending?

14 A Yes.

15 MS. CHIN-CAPLAN: I have no further
16 questions at this time, Special Master.

17 SPECIAL MASTER HASTINGS: All right. Mr.
18 Matanoski, will you be having any redirect for this
19 witness?

20 MR. MATANOSKI: I may well have a little
21 redirect, yes, sir.

22 SPECIAL MASTER HASTINGS: All right. Why
23 don't we take a 15-minute break, at this point, for
24 the afternoon and convene shortly after 4:00.

25 (Whereupon, a short recess was taken.)

1 SPECIAL MASTER HASTINGS: All right. We are
2 going to start our afternoon, the second part of our
3 afternoon activities now. I want to say one thing for
4 those in the courtroom, as I noted at the beginning,
5 our Court has very generously allowed the use of this
6 courtroom by the U.S. Court of Appeals for the Federal
7 Circuit. It is very important that no food or drink
8 be brought into the courtroom at all. Those at the
9 counsel tables and the bench can drink water out of
10 the pitchers. That is it, nothing else in the
11 courtroom, please. We want to be good guests to the
12 Court of Appeals. Although I will say, those at home,
13 you can either drink whatever you want.

14 (Laughter.)

15 SPECIAL MASTER HASTINGS: But with that, Ms.
16 Ricciardella has some redirect examination of Dr.
17 Fombonne. Go ahead, Ms. Ricciardella.

18 MS. RICCIARDELLA: Thank you, Special
19 Master.

20 REDIRECT EXAMINATION

21 BY MS. RICCIARDELLA:

22 Q Dr. Fombonne, Ms. Chin-Caplan walked you
23 through the laboriously certain articles that you have
24 written since June of 2004 and asked you whether or
25 not you included a financial disclosure statement

1 regarding your participation as a consultant to the
2 pharmaceutical companies and the thimerosal
3 litigation. If I am understanding, it is true that
4 only one of those articles, there is no financial
5 disclosure statement, is that correct?

6 A Printed on the article, yes.

7 Q But to be clear, you did not inform the
8 journal editors where that article appeared of your
9 participation in the thimerosal litigation, correct?

10 A Correct.

11 Q And it was their decision not to print the
12 financial disclosure, is that right?

13 A Yes, absolutely.

14 SPECIAL MASTER HASTINGS: Doctor, you need
15 to say a word rather than nodding so we can pick it
16 up.

17 THE WITNESS: Okay. Yes.

18 BY MS. RICCIARDELLA:

19 Q Doctor, there was also some discussion about
20 your participation as a consultant for the
21 pharmaceutical companies in the Easter case in Texas.
22 Do you recall that?

23 A Yes.

24 Q What was the time frame of your
25 participation in Easter? When did you first become

1 involved in the Easter case?

2 A As I said, since June 2004. I had been
3 actually approached before by various -- even when I
4 was in the U.K. to be consulting with that. I denied
5 doing that. And I was not particularly interested in
6 this activity. I researched it when -- years after
7 the MMR controversy given up after the initial
8 Wakefield paper, when I saw -- again, it has to do
9 with the impact at two different levels. I see a lot
10 of families. So, in my clinics earlier last week,
11 people still come and ask questions about safety of
12 vaccines and they asks questions about MMR. They ask
13 questions about mercury. I spend a lot of time trying
14 to give the evidence to the parents and it's very hard
15 to convey, to disseminate this evidence when there is
16 a general rumor or fear of the public. It is hard to
17 counteract. And I've seen that when I was in the U.K.

18 There is a very interesting historical
19 example, which has to do with the whooping cough
20 vaccination. In 1971, there was one study which
21 incriminated the whooping cough vaccination where the
22 neurological design. It was one piece of research
23 released probably in the BMJ. Immediately, people
24 started to be afraid of this vaccination. And what
25 happened is within 18 months of this initial

1 publication, two studies looked at the initial results
2 and basically dismissed, failed to replicate that and
3 dismissed the result. Yet what happened, if you look
4 at the trends over the next 10 years, from '71 to
5 1980, there was a massive drop in the uptake of
6 whooping cough vaccinations in the U.K. And then you
7 could see the notifications of whooping cough disease
8 occurring and there were outbreaks and there were
9 actually death of that. And it took 10 years to put
10 back the vaccine on the agenda, in an effective way.

11 And it's exactly what happened in the U.K.
12 with the MMR vaccine. It was dropped intake, which I
13 mentioned, which has effected public health in the
14 U.K., in Ireland, and it creates a big concern for
15 people. It's a preventable disease. I think you
16 would say that half a million of the people die every
17 year. I recall that there was an epidemic in the U.S.
18 in 1990-1991, when 150 people died from measles. And,
19 again, there was an outbreak 18 months ago in this
20 country. So, unless we keep our eye on these
21 vaccinations, it's very important to -- well, we need
22 to be correcting and maintaining vaccination rates at
23 a high level.

24 Although, at the same time, when the initial
25 concerns were raised, I did research immediately to

1 look at this. So, it's not that I was actually biased
2 against it. I looked at the evidence. There was not
3 much plausibility to start with with the arguments put
4 forward by Dr. Wakefield. But quickly, the research
5 did not give any empirical support to these ideas.

6 So for me, the MRC did a big review document
7 published in 2001 or 2002 in which I was involved,
8 concluding that there was no evidence for this
9 association. But yet, the effect was negative and
10 it's still there. So, when I came here and I saw this
11 concern about thimerosal, which I had been involved in
12 the American Academy of Pediatrics in 1990 when they
13 reviewed this whole issue about TCVs and autism, what
14 happened, we have witnessed a development of, for
15 instance, chelation therapy, which are absolutely
16 based on false ideas, no evidence, are dangerous, and
17 I think it's very important that as autism clinicians,
18 we tackle this issue with the science. There is a lot
19 of scientific evidence which gives no support to this
20 assertion, and we need to disseminate this
21 information.

22 That's why I am. I am here as a clinician,
23 who works with families with autism. Also, I am here,
24 because my background gives me a sort of sensitivity
25 to public health issues, broadly speaking.

1 Q Is that why you are also participating as a
2 consultant to the pharmaceutical companies in the U.S.

3 --

4 A Yes. It's exactly the same.

5 Q -- other financial litigation?

6 A Yes, absolutely.

7 Q Now, Doctor, Ms. Chin-Caplan began her
8 cross-examination of you asking you to acknowledge
9 that the pediatric records in this case of Michelle
10 Cedillo do not mention certain development
11 abnormalities. In your practice, as a child
12 psychiatrist, with a specialty in autism, is this an
13 abnormal finding? Do you have pediatric records not
14 reflect or note abnormal development delays?

15 A Well, it's absolutely true, every clinic --
16 autism clinic, when we see the children at age -- for
17 me now, it's more like two, two-and-a-half, and three,
18 much younger than 10 years ago or 20 years ago, which
19 is good, but still the story is consistent across the
20 families. They go and see GPs, often, as I said
21 before, age 15 months, 18 months, 20 months, and then
22 there is a sort of dismissal of the matter of concern.
23 The child is not speaking. It's true that there is
24 wide individual variability in language development.
25 They say, don't worry. He's going to speak. Then the

1 family comes back three months later, they want to
2 check the hearing. And then it takes like months
3 before the child is referred from the GP pediatricians
4 to -- and understandably. Their level of training to
5 detect autism, it is very limited unless they have a
6 specific interest for that. So they don't detect the
7 signs.

8 And to detect the signs, I hope I conveyed
9 this morning that you need specific expertise.
10 Sometimes it's very obvious, so you might not miss it.
11 But in many, many cases, you need to look at the
12 child and do with him the right things to elicit the
13 autistic symptoms, which means you need to ask
14 targeted questions of the parents.

15 And a pediatric or GP consult with a child
16 who is 12 months or 15 months usually lasts about five
17 minutes, seven minutes. I think you can have seven
18 minutes on average. And they do weight and height and
19 they look at feeding and growth and then that's it.
20 So you understand why it occurs that in the pediatric
21 record, there will be no documentation of
22 developmental issues unless the parents push that on
23 the agenda as a concern of theirs. And actually
24 research, which I should add.

25 So, in the U.K., for instance, this is

1 research, not clinical experience. There are several
2 countries where health records are kept. So at birth,
3 you have the Apgar scores and everything, and the
4 parents have a record, a booklet, and every visit is
5 documented. So we have used that as a tool. There
6 was in the U.K. a study by, I would say Uta Frith, I
7 can find the exact reference for you, where they
8 showed that at six months, at 20 months, in the
9 medical records, there was no documentation of
10 abnormal development in children that later turned out
11 to be autistic. It started to occur about 18 months
12 of age. So what we see in that case is not atypical.
13 It's actually quite average what we see, in terms of
14 the contacts with the health system of these children.
15 It's often delayed. The recognition is delayed due
16 to medical factors.

17 Maybe I want to add something else, which is
18 questions where directed to me, trying to compare the
19 absence of particular behaviors in the medical record
20 to what was the study of young children assessed at
21 six months and 20 months of age, which were done by
22 directed solutions in the lab, by people with
23 expertise to assess the inference with autism. So, it
24 doesn't compare like with like.

25 I mean, on one hand, you have dangers

1 identified by Autism Express who have the eye for that
2 who assess the children directly in interactive
3 sessions. And we cannot infer anything of the absence
4 of these behaviors beings recorded by the
5 pediatricians in sessions which are not directed at
6 developing that and which last for just a few minutes.
7 So I think there is a methodological confound in the
8 questions which we are asked to maybe form.

9 Q Ms. Chin-Caplan also questioned you about
10 your Slide 35, which is the chart of Michelle's head
11 circumference. And then she put on the screen, I
12 believe it was Petitioner's Exhibit 79 and 10, which
13 she seemed to suggested that perhaps you were not
14 taking into account Michelle's growth, at the same
15 time, her height and weight, at the same time that her
16 head was growing. Doctor, in your report, did you
17 address the concomitant weight and height of Michelle,
18 in relation to her head circumference?

19 A I think I did.

20 Q May I direct you to --

21 A I think it was page 54 or 59.

22 Q I believe it was on page 60, paragraph 157.

23 A Thank you. Yes. On that particular -- just
24 let me -- the sentence at the bottom of that page on
25 60, it says, from six to 18 months, the head

1 circumference chart shows clearly that Michelle's head
2 circumference is consistent of the chart and far
3 beyond the 97 percentile, that difference macrocephaly
4 with a maximum rate of head growth in the second
5 semester of life. This abnormal head growth cannot be
6 certainly attributed to the general overgrowth
7 syndrome displayed by Michelle, shown in her length
8 and her weight curves, as the head circumference
9 abnormal growth clearly exceeds that of the length.
10 This pattern has been described in the chapter on
11 autism. And I quote a study by Lainhart et al. I
12 would like actually to -- if I could show you some
13 figures, which are from the circumference. If you
14 could --

15 Q Do you have a slide for that?

16 A I have a slide for that, yes. This one.
17 This is a large study done by, again, a group of
18 autism experts. It is part of the CPA network of
19 research in the U.S. And they gathered also the
20 information on the head circumference and looked at it
21 in various ways. And on the top left graph is a
22 standardized head circumference in this sample. And
23 you see on the central axis, there is a zero. Zero
24 should be the mean of the population. So, there
25 should be a normal curve that we have. We should be

1 centered on the mean, which would be zero, because we
2 are using standardized scores. But, in fact, the
3 means of the autistic samples, as you can read on the
4 right of this graph, is I think 0.65. That means that
5 on average, there is a shift towards the right of the
6 distribution of head circumference in the autism.
7 There are larger heads on average, and it's shifted to
8 the right by two standard deviations, which is
9 substantial.

10 On the bottom left, you see just a graph
11 which indicates the relationship which exists between
12 head circumference and height, and you can see there
13 is a strong correlation between the two. These are
14 the standardized scores. So what they did therefore
15 was to look at if we take into account the height of
16 the subjects, the body length, which is correlated
17 with head circumference, do we still have an -- seen.
18 And this is what the graph on the bottom right shows.
19 It's a graph which says -- basically it's a
20 standardized score of head circumference minus the
21 standardized scores of height. So it is therefore a
22 quantity which takes into account the body length and
23 looks at head circumference, adjusting for height.
24 And still you find that there is actually -- the
25 division in the right of this variable is still the

1 Respondent's Trial Exhibit
2 No. 9 and was received in
3 evidence.)

4 MR. MATANOSKI: Yes, Special Master. Dr.
5 Fombonne had much more evidence than presented here.

6 SPECIAL MASTER HASTINGS: Okay.

7 MR. MATANOSKI: We pared it down to what we
8 thought was necessary for your consideration.

9 THE WITNESS: I think for reference, these
10 graphs are extracted from the study by Lainhart, L-A-
11 I-N--H-A-R-T, 2006, *American Journal of Human*
12 *Genetics*.

13 BY MS. RICCIARDELLA:

14 Q Now, Doctor, Ms. Chin-Caplan also asked you,
15 she said, do you accept that Michelle had 10 words,
16 and she was referring to paragraph 155 of your report.
17 You said that Michelle had 10 words?

18 A No. No, I do not show that. To you, she
19 might appear that she had 10 words. They were saying
20 that she would use consistently word meaning
21 spontaneously 10 words by then, and this is based on
22 two obvious line of evidence: the video, which she
23 showed at 15 month-and-a-half, where she produced
24 absolutely no words when she is playing with the
25 balls, and she has even very little babble, which is

1 not used communicatively, clearly indicates that
2 whatever words she might have pronounced in the few
3 weeks before that would have been very haphazard or
4 random. So, I think that's -- and secondly, I think
5 Michelle's mother, in her testimony last week, listed
6 a few words, not even 10, and there was no evidence of
7 a language in the child before the MMR.

8 Q Finally, Doctor, one last question. Ms.
9 Chin-Caplan asked you why you had selected the
10 February 6, 1996 video as evidence to show Michelle's
11 motor delay, and she made point of the fact that that
12 video was following the MMR vaccination. Why did you
13 select that video as evidence of her motor delay?

14 A Because it's one which shows that she
15 doesn't work independently. I am not aware that the
16 Plaintiffs are saying that MMR triggered motor
17 deficits in Michelle. So wherever we see that, it's
18 just the smooth continuation of a motor development
19 and it shows delay at that age, as there is evidence
20 of delay at much earlier stages in her development.

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

23 SPECIAL MASTER HASTINGS: Let me ask, while
24 we are on that topic, did you see any of the earlier
25 videos? You looked at all the videos that were

1 supplied by the Petitioner. Was there any evidence of
2 unassisted walking at any time prior to that?

3 THE WITNESS: Never, never.

4 SPECIAL MASTER HASTINGS: Okay. Go ahead.

5 MS. RICCIARDELLA: I have no further
6 questions, Special Master.

7 SPECIAL MASTER HASTINGS: All right. Thank
8 you, Ms. Ricciardella. Anything further for this
9 witness, Ms. Chin-Caplan?

10 MS. CHIN-CAPLAN: No, Special Master.

11 SPECIAL MASTER HASTINGS: Anything from the
12 other Special Masters? I think I may have had --
13 well, on that very topic of the walking, what is the
14 normal -- when do children normally walk?

15 THE WITNESS: There is variability, but
16 beyond 16 or 17 month of age, it would be concern that
17 the child is not walking independently. That is
18 clear. And I said in the 18 month of age, if the
19 child is not walking, it is clearly a sign of a
20 problem. She is seventeen-and-a-half month there and
21 she doesn't have independent walking. Again, if you
22 look at the milestones earlier than that, sitting
23 independently at 11 months is extremely delayed.
24 Children usually sit independently between six and
25 seven months of age. At eight months of age, we would

1 consider that to be a significant delay.

2 SPECIAL MASTER HASTINGS: One further
3 question, then. Most of the questions that I have
4 written down here have been asked, it looks like.
5 But, the clinical treatment of somebody with autism,
6 who typically sees autistic children? What
7 discipline? Now, you are a psychiatrist. I've seen
8 neurologists listed. Who is the one -- what is the
9 specialty that most often deals with autism children?

10 THE WITNESS: In terms of treatment? In
11 terms of --

12 SPECIAL MASTER HASTINGS: In terms of
13 treatment, evaluation and treatment.

14 THE WITNESS: Okay. These are two different
15 facets.

16 SPECIAL MASTER HASTINGS: Okay.

17 THE WITNESS: In many centers, now, you have
18 teams, which are an autism expertise for the
19 evaluation, diagnosis, and assessment, initially of
20 these children. And these teams are all
21 multidisciplinary in nature. So, it's always
22 involving different disciplines. You need speech and
23 language therapy. You need occupational therapy. You
24 need child neurology. You need medical genetics, at
25 times. You need pediatrics. You need psychiatry.

1 You need psychology. So, you need all of that
2 discipline. So the people who are leaders, clinical
3 and academic leaders in the field, actually come from
4 very different disciplines. Many of my best
5 colleagues in the U.S. are actually developmental
6 clinical psychologists, who are leading teams which
7 are assessing, diagnosing children with autism. They
8 are consultant in neurologist and they consult
9 geneticists. Others are led by child neurologists.
10 Others are led by developmental pediatricians. Others
11 are led by child psychiatrist.

12 So it depends on the organization of
13 services, the history of service in a given hospital
14 or institution. But the problem is that whatever is
15 the discipline, all these people in addition to their
16 background training have specific training, interest,
17 and expertise in autism, which is added to their core
18 training. And there are different disciplines which
19 are brought in in assessing the child.

20 If you then refer to treatment and
21 management, that's variable. It depends on which kind
22 of services are available. In many countries, it's
23 really people who have an educational background or a
24 psychology background who are doing behavioral
25 interventions. So they would be psychologists who

1 have an interest in behavioral management or
2 educational psychologists or people of that kind.

3 And they put programs which are
4 individualized which take into account the strength
5 and deficits of the child as targets to the treatments
6 so that the child can be promoted in his development
7 in different domains. Treatments are reviewed very
8 periodically to address the goals. Treatment teams
9 work closely with parents who know their child and
10 there is a need to have a flow of information both
11 ways.

12 And then at that time, when the child is
13 moving in the educational and parental system, the
14 contribution of medical disciplines become less
15 significant often except that we provide specific
16 expertise, for instance, in managing complex
17 behavioral problems with particular medications or for
18 medical care. On my team, we have pediatricians who
19 have a specific interest for the medical issues of
20 children with autism. So any medical issue, she is
21 here and she has -- if required.

22 SPECIAL MASTER HASTINGS: All right. Thank
23 you, Doctor. We appreciate your testimony. You're
24 done for the day. I understand we'll see you again
25 next week.

1 THE WITNESS: Yes, thank you.

2 SPECIAL MASTER HASTINGS: Thank you.

3 (Witness excused.)

4 SPECIAL MASTER HASTINGS: Mr. Matanoski,
5 shall we start with Dr. Cook?

6 MR. MATANOSKI: Yes, we're ready to do that,
7 sir.

8 SPECIAL MASTER HASTINGS: All right.

9 Whereupon,

10 EDWIN COOK

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

13 SPECIAL MASTER HASTINGS: Okay. Ms. Patton,
14 please go ahead.

15 DIRECT EXAMINATION

16 BY MS. PATTON:

17 Q Dr. Cook, can you state your name and
18 current place of employment for the Court, please?

19 A Edwin H. Cook, Jr., M.D. I am at the
20 University of Illinois at Chicago.

21 Q Have you ever testified in court before?

22 A Yes, on several occasions. The notable ones
23 are, I testified on behalf of patient with catatonia,
24 who needed electroconvulsive therapy. Even though his
25 parents and guardians agreed, in the State of

1 Illinois, it requires court agreement to that. So, a
2 guardian ad litem advocated actually against the
3 electroconvulsive therapy, but the judge found in
4 favor of the treatment, and he had a successful
5 treatment.

6 Another occasion was actually on court order
7 that we requested. University counsel actually tried
8 to avoid me basically being forced to testify about
9 one of my patients and her mental state. I was
10 required to testify, because it involved child custody
11 of her grandchild.

12 Q Any criminal cases?

13 A Oh, yes. A criminal case in which I was an
14 expert for the defense in defending a young woman, I
15 guess she had just turned 18, when she was accused of
16 attempted murder.

17 Q To your knowledge, have you testified in any
18 lawsuits?

19 A Not to my knowledge or recollection.

20 Q Do you hold any patents, Dr. Cook?

21 A Yes. I hold a patent. It's a
22 pharmacogenetic patent for actually a drug that is the
23 first drug pharmacogenetic patent. In other words,
24 it's the first time in the PDR that a gene is linked
25 with a drug treatment. It relates to my work as a

1 molecular genetic core director for a cancer
2 pharmacogenetics research grant. In the process of
3 supporting that, there's a relationship between the
4 gene UGT1A1 and treatment of colon cancer with
5 RonoTCAN. I'm listed as a co-holder of the patent but
6 do not receive royalties or any other benefits.

7 Q No financial benefits from that patent?

8 A No financial benefits.

9 Q To your knowledge, do you have any financial
10 conflicts of interest that would influence your
11 testimony about the role of genetics in autism here
12 today?

13 A I do not have any specific conflicts
14 relating to what I am going to testify about.

15 Q Okay. Let me turn to your educational
16 background now for a moment. Can you, please, tell
17 the Court what degrees you hold and from where you
18 received those degrees?

19 A I received a Bachelor of Arts from Southern
20 Methodist University in biology and a medical degree
21 from the University of Texas Medical Branch of
22 Galveston.

23 Q And when did you receive your medical
24 degree?

25 A 1981.

1 Q And where did you complete your residency?

2 A I went to the University of Chicago, where I
3 completed my residency in psychiatry.

4 Q Did you hold any honors or any special
5 positions during your residency?

6 A I was the chief resident.

7 Q And after residency or towards the end of
8 it, did you do any specialization or any fellowships?

9 A Right. So, I, also, completed fellowship
10 training in child and adolescent psychiatry.

11 Q Are you board certified?

12 A Yes. I'm board certified in psychiatry and
13 also board certified in child and adolescent
14 psychiatry.

15 Q Do you have any other roles in the board
16 certification process?

17 A I have several times served on the -- I have
18 participated in the examination of candidates for
19 board certification in child and adolescent
20 psychiatry, in which we would conduct an oral
21 examination, in which they would interview a live
22 patient, and we would evaluate whether they performed
23 adequately, in terms of the evaluation of the patient,
24 and in the use of that information.

25 Q What is your current position at the

1 University of Illinois at Chicago?

2 A I am a professor of psychiatry. I am also
3 the visiting director of autism and genetics.

4 Q And when did you start there?

5 A In 2005.

6 Q And within the University of Illinois at
7 Chicago, there is a special center that you work at?

8 A Yes. Within the Department of Psychiatry, I
9 worked in the Institute for Juvenile Research, which
10 will be having its 100-year anniversary, and two years
11 as the first University-based clinic -- actually, the
12 first child psychiatry clinic in the country.

13 Q And what is done at the Institute for
14 Juvenile Research?

15 A We take care of patients with a range of
16 child and adolescent psychiatric disorders. Autism
17 is certainly one of the emphases, but we see a whole
18 range of child and adolescent psychiatric disorders.
19 We, also, train -- we train medical students there,
20 residents and fellows after their medical training,
21 and also train people, and we consider postdoctoral
22 fellows and research as well.

23 Q You said you train a lot of people. Do you
24 teach --

25 A I teach --

1 Q -- at the University?

2 A Yes, I'm sorry. I teach the introduction to
3 human genetics part of the introductory genetics
4 course for the graduate students in biology at the
5 University. I, also, supervise residents and fellows
6 and also mentor both at the University of Illinois at
7 Chicago and across the country, several research
8 faculty.

9 Q Have you ever diagnosed and treated a
10 patient with autism?

11 A Yes, since approximately 1984.

12 Q Do you have any idea in the course of your
13 career how many patients you have diagnosed and
14 treated with autism?

15 A I would estimate in terms of evaluation and
16 diagnosis about 1,000; in terms of treatment, probably
17 several hundred, I would say around 300.

18 Q Do you currently see patients with autism?

19 A I currently have the clinic and follow
20 patients, some of whom I've seen for over 15 years. I
21 have two clinics a week, largely following up patients
22 over a long term, but also conducting new evaluations.

23 Q And these patients that you see in clinic,
24 are they involved with your research?

25 A Well, my clinic, they may have been research

1 subjects. But, we, also, conduct, during the rest of
2 the week, I'm involved in research diagnostic
3 evaluations, as part of our research studies,
4 primarily genetic research studies.

5 Q So, two days a week, you have clinic, where
6 you're actively involved in the treatment of autistic
7 patients?

8 A That's correct.

9 Q And then the rest of your time is spent on
10 research?

11 A That's correct.

12 Q Is that research primarily research on the
13 genetics of autism?

14 A It's primarily on the genetics of autism and
15 also includes work, as I mentioned before, where
16 because of my genetic expertise, I'm helping
17 colleagues study the pharmacogenetic of cancer, both
18 colorectal cancer and childhood leukemia, in terms of
19 the genetics expertise, and also involves continued
20 work that we've been doing in terms of ADHD genetics.

21 Q When did you began research or working in
22 the field of autism?

23 A In 1985, in the second year of my
24 fellowship, I began studying serotonin and it's
25 relationship to autism.

1 Q And in what areas has your research focused?

2 A It's gone through various phases, starting
3 with studying neurochemistry. I chose to study
4 serotonin autism, because having looked at the
5 literature, it was a finding that had restored much
6 test on what might possibly be an artifact, in terms
7 of a portion of children with autism having high blood
8 serotonin. We conducted and continue to conduct
9 careful studies to understand the mechanism of that
10 elevation. We know the elevation is there, but we
11 haven't tied it sufficiently cleanly to exactly what's
12 happening in the brain yet, which, of course, is the
13 ultimate goal.

14 In the process of those findings, it became
15 clear that the findings in the blood were likely
16 giving us clues as to mechanisms in the brain and what
17 was likely is that there were genes expressed in the
18 blood, specifically in the platelet, that were also
19 expressed in the brain. And so, genetics provided us
20 a clue as to what might be leading to a symptom or a
21 sign in the periphery that also was more directly
22 relevant to brain development. So, around 1993, we
23 shifted to not only studying serotonin as a chemical,
24 but also studying serotonin genes in relationship to
25 those chemical changes.

1 Q So, that was the neurochemistry. And then
2 clinical pharmacology, you've been involved in that?

3 A Well, the best question about clinical
4 pharmacology is why do I do -- or why do I look a
5 group studying chemistry and genetics, and that's
6 because the ultimate goal are better treatments for
7 autism. And it is almost certain in those treatments,
8 in least in terms of what I can provide, there are
9 many other people, who can provide much better
10 behavioral and educational therapies and improvements
11 in those areas, but in terms of my role as a medical
12 researcher, personally, I want to develop the very
13 specific mechanistic understanding that will lead us
14 to much better treatments for autism targeted to the
15 mechanism of the disorder.

16 Q On Dr. Fombonne's direct, he had a chart of
17 different treatments that had been tried and failed
18 with autism. One of those was secretin. Were you
19 involved in those trails?

20 A Yes. We have been involved in trials of
21 medications that are available for other treatments
22 and trying to see if they would be helpful for autism.
23 And because we had developed that expertise on
24 clinical trials, when, as Dr. Fombonne mentioned,
25 there was a possibility that in a sense someone had a

1 sort of lucky finding, that perhaps secretin might be
2 helpful to autism, because of the three case reports.
3 We understood the importance of that and as opposed
4 to this sort of previous thing that had happened right
5 before secretin was facilitated communication. We
6 weren't able to help in studying facilitated
7 communication, but somebody else had the expertise to
8 under -- to test does it work or does it not work.
9 Because, of course, I understand how important it is
10 for these things to be studied and I personally feel
11 the desperation for us to have better treatments
12 today.

13 And so, I had to sort of stand by as
14 facilitated communication went through the phase of
15 being a fad, where everybody was doing it. People
16 were being falsely accused of abuse. Parents were
17 being falsely accused of abuse. But, then, to see
18 somebody put it to the test and then became
19 discredited. Secretin was -- we were in the -- we
20 then had the opportunity to test it quickly.

21 Now, one could have the impression, the way
22 that I'm saying this, that the goal of testing it was
23 to show it didn't work. But, I actually have a very
24 strong conviction that our research resources should
25 not be directed to things where going in, we don't

1 think they're going to work. So, yes, there were
2 these exciting case reports and we had the resources
3 to test secretin versus saltwater. And I was very
4 proud that within a few months, we were able to
5 conduct this study, which I thought had high public
6 health importance, given how many people were
7 receiving it. And we put it to the test and, frankly,
8 we were excited, because some children looked better
9 after the study. Of course, we were carefully
10 blinded. Secretin is actually something that's fairly
11 easy to blind. And I was disappointed when saltwater
12 was slightly better than secretin.

13 This is not what one looks for. And I am
14 very aware that some of our best medication treatments
15 have come from the kind of luck that led to secretin.
16 But, it didn't hold up to the test of was secretin
17 better than placebo. Interestingly, all the children
18 got better and it wasn't because we were somehow
19 wanting them to get better and not being careful
20 scientists. I think we had a large group of families,
21 who were desperate and feeling the hope that secretin
22 was providing on the time, provided parents, who were
23 much more -- everybody around the child was just more
24 upbeat, because at least momentarily, it was helping
25 people with the understandable process that people

1 have to work through, in terms of having a child with
2 any kind of serious problem. It's really a grief
3 process that eventually -- and it's a difficult time
4 and the parents, who were coming to see us, were in
5 great despair and at least momentarily were much more
6 hopeful. What I hope is that eventually they work
7 through that process, accept their children for who
8 they are, and I know the parents do. It's a difficult
9 time for parents in the very early years.

10 Q What initially made you decide to focus your
11 study or research on autism?

12 A Well, that's pretty easy. When I was six,
13 my younger brother was born. There was some
14 difficulty around his birth. But, basically, we
15 thought he was doing okay for about six months. Then,
16 we knew there were problems for another, I would say
17 12 months. And I do remember acutely when my parents
18 decided that something was definitely going on and it
19 was when my mother took my brother over to visit one
20 of her friends, who had an 18-month old child, and the
21 contrast was stark. So, if you ask my mother and
22 father now when something started, they would say six
23 months or even wonder about the first six months.
24 But, it's understandable, one has hope that what one
25 is seeing would just sort of go away and children will

1 'go back to a normal pathway.'

2 So, anyway, my brother had -- wasn't
3 responsive to people very much in the early years of
4 his life and also had the characteristic
5 preoccupations with people with autism, many of which
6 I fondly remember. You wouldn't know this today. You
7 would have to have a different preoccupation, I
8 suppose, but he could find exactly what track on the -
9 - which groove on a record had what point of a Sesame
10 Street or Mr. Rogers passage he wanted to see.

11 One of the reasons I bring this up is that
12 he -- no one ever thought that he had autism yet, like
13 today's classification and criteria. He would be
14 thought of as one of the most severe cases. So, it's
15 somewhere around the time I was 10, just seeing how
16 much pain it was causing my parents, I think, and the
17 struggles -- and his struggles, frankly, was a sort of
18 childhood wish to try to do something about this.

19 Q And when did you start focusing -- or why
20 did you start focusing on the genetics of autism?

21 A The chemistry work that we had done leading
22 up to 1993, actually, it was a failed grant review,
23 where we were studying platelet serotonin and
24 basically it was a grant review, a grant we eventually
25 did not receive, where they said the only logic of the

1 platelet being involved in autism would be a gene that
2 was expressed in the platelet brain. We shifted that.
3 We, also, had findings in the chemistry that said the
4 next step was to look for mutations in the genes that
5 were leading to the chemistry changes. And, as a
6 matter of fact, it was really more of a colleague that
7 found that recently. Jim Sutcliffe found in a pretty
8 classic *American Journal on Human Genetics* paper that
9 certain people with autism have specific mutations in
10 the serotonin transporter. And one of our earlier
11 chemistry findings had been that some patients with
12 autism had very increased serotonin transport
13 function.

14 Q And that is what initially sparked your
15 interest in the genetics of autism?

16 A There was some hope that genetics would
17 somehow deal with the fact that autism is a very
18 heterogenous syndrome, as mentioned by Dr. Fombonne.
19 To tell you the truth, if one really thinks about it,
20 genetics has as much trouble with heterogeneity as
21 anything else. I must say that the same reason that
22 we were attracted to the serotonin finding is why we
23 were attracted to the genetics finding, because it
24 became very clear that genetics, as a discipline, has
25 an approach where, as opposed to other things that we

1 might learn about the brain in autism, that you might
2 not know what was chicken and egg, what came first, in
3 genetics, there's a much more direct idea about
4 causation when you do genetics, as opposed to
5 correlation alone.

6 Q Now jump back to your CV for a moment here.
7 Are you on any editorial boards?

8 A I'm on several: the editorial board for
9 *Biological Psychiatry*, the *Journal of Child and*
10 *Adolescent Psychopharmacology*,
11 *Neuropsychopharmacology*, and have recently accepted an
12 appointment as a corresponding editor for the new
13 *Journal of Autism Research* that will be published the
14 International Society of Autism Research.

15 Q Do you have any other positions that would
16 be relevant to your testimony today?

17 A I am also the co-chair of the American
18 Academy of Child and Adolescent Psychiatry, Autism,
19 and Intellectual Disability Committee.

20 Q What is that committee?

21 A So, it's for the organization, the American
22 Academy of Child and Adolescent Psychiatry, which is
23 the professional organization of American Child and
24 Adolescent Psychiatrist, and the committee is composed
25 of people interested in caring for and studying people

1 with autism and intellectual disability, formerly
2 known as mental retardation.

3 Q Do you or have you served on any autism
4 advisory boards?

5 A I was one of the first members of the Peer
6 Autism Now Scientific Advisory Board and served for
7 several years and, also, served for one year as the
8 chair of the Scientific Advisory Board.

9 Q What was your role as chair of that advisory
10 board?

11 A I would help organize and conduct the
12 scientific review of research proposals to the
13 organization.

14 Q But, you're no longer on the advisory board?

15 A That's correct.

16 Q Have you been directly involved in genetic
17 studies related to autism?

18 A Yes, since 1993.

19 Q Okay. I note on your CV that there appears
20 to be over 150 published peer review articles on
21 autism. Does that sound correct?

22 A I think there's over 150 in general. There
23 would be less specifically pertaining to autism. So,
24 that would include ones on ADHD or even ones on cancer
25 pharmacogenetic.

1 Q Of those articles, do you know about how
2 many were peer reviewed publications on the genetics
3 of autism?

4 A Certainly over 30.

5 Q I think we counted 60, but I think over 30
6 counts in there. What has been your involvement in
7 those studies?

8 A It's ranged from studies that we propose
9 that only included subjects from our particular
10 university and laboratory, in which the subjects were
11 recruited, evaluated at our site, and in which the
12 laboratory studies were conducted in my laboratory.
13 And it has ranged all the way up -- there are several
14 levels of studies, in which we might collaborate with
15 three or four other groups, studies at the level of
16 the International Molecular Genetic Study of Autism
17 Consortium, that includes dozens of investigators from
18 several countries in Europe and North America, all the
19 way to the participation of that consortium and what
20 we consider the consortium of consortia, the Autism
21 Genome Project, which includes over 100, well over
22 100, investigators and many more people who are
23 involved in the study in some role.

24 Q Why do you believe so many geneticists are
25 drawn to the study of autism?

1 A It actually came from a paper in the 1990s,
2 in which Pullman published in science a comparison of
3 estimates of heritability of autism compared to other
4 disorders that people were very interested in,
5 disorders that might not even be as common, such as
6 Type II diabetes, such as Type I diabetes, such as
7 asthma, such as hypertension, such as coronary artery
8 disease. And what they found was that the
9 heritability was much, much higher for autism than
10 those other disorders, in which a lot of geneticists
11 were working on. So, I think they've basically been
12 drawn into it, in terms of seeing it as a scientific
13 opportunity.

14 Q Why do you continue to spend so much time on
15 the genetics of autism?

16 A It's an outstanding question, because I feel
17 very much drawn to do the things that maybe not
18 everyone else is doing. I've commented on several
19 venues about some of my own autism-related traits and
20 I suppose going and doing something different might be
21 one of those. So, the fact that there are so many
22 people working on the genetics of autism and, frankly,
23 so many giants outside of the field of autism genetics
24 coming into autism genetics makes me think, well,
25 that's really what we want happening for our children,

1 adolescents, and adults with autism, and their
2 families. We want to bring people in to study autism,
3 because it's so important.

4 Why do I continue to do it? I suppose
5 because I still go back to the perspective of the
6 brain is so complex in studying it. We have that as a
7 problem. And even when we go into the brain studies
8 and we find abnormalities, we don't know whether they
9 might be three or four levels down the line,
10 particularly if we're studying, as I hope, that we
11 don't have brains to study until people are ideally
12 the same ages when everybody else passes away. We
13 don't want people to pass away early and have their
14 brains to study. But even if we have brains at five,
15 what was happening was thought to largely be prenatal.
16 So, you have this problem of what you're studying,
17 this whole chicken and egg problem.

18 And the other problem, frankly, is that we
19 need to study brains. There aren't that many to
20 study. There are many more. I'm working to try --
21 work with the autism tissue program and with Margaret
22 Bauman's tissue program, to try to help with that
23 situation, in terms of having people study the brains
24 that are available. But the reality is that through
25 genetics, we can study genes that are having effects,

1 in terms of brain development, from thousands or
2 eventually tens of thousands of people while they're
3 alive.

4 Q Do you think that research on the genetics
5 of autism may eventually lead to some treatments for
6 autism?

7 A Well, that is the goal. And I think that we
8 -- so, right now, as a matter of fact, it was
9 mentioned before the Fragile X Syndrome is one of the
10 genetic causes of autism in a few percent of cases.
11 Taking the other direction, 25 to 50 percent of people
12 with Fragile X, depending on how you define it, have
13 autism. That gene was cloned, Fragile X gene was
14 cloned in the early 1990s and it's very easy in 2007
15 to go, oh, we cloned the gene. We can diagnose it,
16 but what else can we do with it. And, believe me, I
17 don't want us to pretend that we can do more than we
18 can. We have to be honest about our limitations. I
19 am excited, though, that through 16 years of basic
20 science, with that information from that gene, that,
21 for example, a model in fruit flies have been created.
22 A model in mice has been created, and not by
23 correcting the genetic defect per se, but by
24 understanding how it effects signaling between nerve
25 cells. There are now methods that will improve

1 behaviors in those animal models. And as a matter of
2 fact, we are now working with a company called Seaside
3 Therapeutics, to be thinking about the first trials of
4 drugs basically moving up those models and with that
5 very specific information, to be doing clinical trials
6 in autism that come from that specific genetic
7 information.

8 Now, I would not want anyone to mistake my
9 excitement that that's coming along, to say that we
10 know it's going to work, because we don't. In fact,
11 we've tried a couple of -- we've been involved in a
12 clinical trial with what's called an ampikine that
13 uses a related approach to treatment that, frankly,
14 wasn't effective. It was helpful, though, because now
15 we had done the trial that sets the stage for those
16 later trials, that if we do have something that's
17 effective, we will know how to test through that
18 effectiveness.

19 Q Let me turn now to a couple of terms and ask
20 you how you would define or use those terms. How
21 would you define the term 'possible?'

22 A Well, possible has some meanings, but I
23 generally think of possible as could happen on pretty
24 imaginative persons. So, possible doesn't tell us
25 much. Possible could be things such as the earth

1 possibly is the center of the solar system.

2 Q So, just about anything is possible?

3 A Yes.

4 Q Do you believe that it's possible that
5 individuals can be genetically predisposed to react to
6 thimerosal and/or MMR vaccine, in such a way to cause
7 or trigger autism?

8 A It's less possible than the earth being the
9 center of the solar system.

10 Q Petitioners' experts and Petitioners have
11 focused on the term 'plausible.' And Mr. Matanoski,
12 this morning, in his opening, talked about plausible.
13 How do you define that term or how do you use the
14 word 'plausible?'

15 A Well, I think plausible, I would say, has to
16 be a reasonable possibility. So, it may be how many
17 people think of possible. But, plausible, to me, and
18 the terms I use it are not the way it was defined
19 earlier. Plausible does not mean probable to me.

20 Q Okay. Do you believe that it's plausible
21 that vaccines or one of their components can trigger
22 something in genetically predisposed individuals to
23 cause them to develop autism?

24 A No.

25 Q Dr. Kinsbourne, on Friday, used the term

1 'reasonable medical probability.' Would you need to
2 believe that something is more likely than not, in
3 order to describe it as having reasonable medical
4 probability?

5 A At least that. Because of an important
6 tradition in medicine to do no harm, I think that
7 reasonable medical probability has to be higher than
8 just slightly more probable than not.

9 Q Based on your previous answers, I would
10 imagine that you don't believe there is evidence that
11 a vaccine or vaccines has actually been demonstrated
12 to cause autism in genetically susceptible
13 individuals. Would that be right?

14 A That's correct. I don't actually even know
15 of a specific test of that possibility.

16 MS. PATTON: I am going to pause for just a
17 minute. We have two slides we have and I have the
18 handouts.

19 (Pause.)

20 SPECIAL MASTER HASTINGS: Did you have one
21 for the court reporter? I don't know if there is any
22 hard words in this one, but -- perhaps not. It
23 doesn't look like it.

24 BY MS. PATTON:

25 Q Dr. Cook, in your report, you say that

1 autism is a strongly genetic disorder. Does that
2 primarily come from twin studies?

3 A Yes. This is actually the sort of data that
4 I alluded to in terms of Pullman publishing this data
5 in science and attracting many geneticists in the
6 field.

7 Q Let me turn to your slide for a moment.

8 SPECIAL MASTER HASTINGS: Before you do,
9 just for prosecuting purposes, let's mark this as
10 Respondent's Trial Exhibit No. 10, and we can refer to
11 it that way.

12 (The document referred to was
13 marked for identification as
14 Respondent's Trial Exhibit
15 No. 10 and was received in
16 evidence.)

17 SPECIAL MASTER HASTINGS: So you now are
18 going to go to page 1 of that, I assume?

19 MS. PATTON: Yes.

20 SPECIAL MASTER HASTINGS: Go ahead.

21 BY MS. PATTON:

22 Q One in five children have autism. How is
23 autism defined in that?

24 A One in 500.

25 Q One in 500. How is it defined there?

1 A This is according to a narrow definition, so
2 it would be according to saying *DSM-IV*, autistic
3 disorder. It would not be saying what's the number
4 for autism spectrum disorder. But, this would be the
5 narrow autistic disorder.

6 Q Would that rate go up significantly, if you
7 included the broad autism spectrum disorder?

8 A If you include the whole spectrum, it would
9 go up to somewhere around one in 160.

10 Q What is the evidence? If you could explain
11 through your slide, what is the evidence that genetic
12 -- excuse me, that autism is a strongly genetic
13 disorder?

14 A Right. So, the first evidence is just one
15 step and that is if one child has autism and the same
16 couple has another child, there's about a five percent
17 chance the next child will have autism. First of all,
18 this is a 25-fold increase relative to the one in 500
19 in the population. Given many things run in families,
20 the twin study becomes much more important, because
21 identical twins and fraternal twins are exposed to
22 largely the same environment as each other, but they
23 share very different amounts of genetics similarity.
24 So, if one identical twin -- so, in this case, an
25 identical twin shares 100 percent of genetic variation

1 with the other identical twin, whereas a fraternal
2 twin only shares half of the genetic variation across
3 the genome. So, in a sense -- and the other thing to
4 recognize is a fraternal twin, from a genetic
5 perspective, is the same as a sibling or brother or
6 sister, in terms of 50 percent sharing.

7 So, the idea is that if the increase, for
8 example, one in 500, to five percent is related to
9 environmental factors, then you would see the
10 identical twins having a five percent chance of autism
11 or if one has autism, the other one has it five
12 percent of the time, and for the fraternal twin, if
13 one had it, the one of it would have it five percent
14 of the time would not go up, because of the sharing of
15 50 percent of genetic variation to 100 percent.

16 In the case of autism genetics, from the
17 narrow definition of autism, if one identical twin has
18 autism, there's a 60 percent chance the other
19 identical twin will have autism. This is now a 300-
20 fold increase over the general population. And it's
21 also interesting to note, this is not just a doubling
22 of the 25-fold increase to say 50-fold increase, but
23 this is what's called the multiplying of risk. It's a
24 strong signature, that not only is it strongly
25 genetic, but that it's multiple genes interacting

1 together, when you go from such a low number like five
2 percent. It's also probably included interacting
3 genes, all the way up to 300 fold just from the
4 doubling of sharing genetic variation.

5 Now, sometimes, people go well, where
6 there's 40 percent that did not share autism. It's
7 important to note that over 90 percent of the
8 identical twins, where one has autism, that over 90
9 percent of the time the other identical twin will have
10 significant social impairment. Let me put that in
11 perspective.

12 A For example, in the study of Bailey and
13 colleagues in '95, that out of 25 people they were
14 following up, only two had employment, competitive
15 employment which required substantial social skills,
16 and only one had a confiding relationship by adulthood
17 or was married. The others, it wasn't just that they
18 weren't married. They didn't have evidence of a
19 longstanding, intimate relationship.

20 This is in contrast to disorders where
21 people are focusing quite a bit and for a good cause
22 on genetics such as schizophrenia where there actually
23 are unaffected identical co-twins. And autism, these
24 reports are interesting because in a sense, you can
25 see there was one of the 25 that by a broader criteria

1 wasn't affected.

2 It's also very interesting that some of the
3 environmental risks for some of these were one of the
4 five where they didn't both have autism. Of the ones
5 that did have autism, they had environmental
6 influences around the time of birth or before, which
7 included things like cardiac arrest in the neonatal
8 intensive care unit, included extreme prematurity
9 relative to the other twin.

10 Okay. So now of course if they fraternal or
11 what was referred to earlier as dizygotic twin who are
12 only sharing 50 percent, if they also had a dramatic
13 increase, we would be thinking about environmental
14 effects of being twins, but in this case, there's no
15 increased risk in autism for fraternal twins relative
16 to siblings. And this signature of a very relatively
17 high risk for identical twins relative to fraternal
18 twins is exactly why so many people who aren't really
19 interested in autism but are interested in genetics
20 have started to study it.

21 Q You touched upon it briefly, but back to the
22 identical twins. They share 100 percent, close to 100
23 percent, of their genes. You had said cardiac arrest
24 or other things around birth. Would that be referred
25 to as environment, environmental factors?

1 A Right. So the estimates from the data that
2 you see here put all together into models are genetic
3 factors over 90 percent, 90 to 92 percent, and then
4 there's 8 to 10 percent that's nongenetic. And then
5 the question is, what is that 8 to 10 percent that's
6 nongenetic? Some it is what we would call random.

7 In other words, the brain once there's risk,
8 there's a lot of preprogramming in the brain, but a
9 lot of the reason we can do what we can do is that
10 we're not rigidly, our brains are not rigidly,
11 constructed. So when there's a risk or a
12 vulnerability from, for example, a genetic risk, there
13 are still some random factors in terms of what happens
14 there. It's not all left over as environmental.

15 But then, yes, my point about this paper had
16 a lot of emphasis on whether there were obstetrical
17 environmental risks and prenatal environmental risks.
18 So when we think of environment and gene interaction,
19 particularly in very early child onset, we're very
20 typically focusing in on what happens before birth.

21 Q So gene environment interaction as that's
22 often used in the papers, that doesn't necessarily
23 mean what I as a layperson -- when I think of
24 environment, I think of the outside world around us,
25 far beyond postnatal, things like heavy metals, as

1 Petitioners are referring to. But in these papers,
2 gene environment, is that environment often or most
3 commonly referring to the prenatal environment?

4 A Most commonly. I think people are open to
5 when we think about environment, just off the top of
6 my head and it would take us a while for me to go
7 through them, but I'm sure we're thinking of hundreds
8 if not at least 1,000 different possible environmental
9 factors, among which hundreds would be prenatal,
10 hundreds would be perinatal, and relatively much less
11 likely for let's say people in the United States would
12 be postnatal environmental factors, but they're
13 possible in the sense of anything is.

14 Q In his report, Dr. Kinsbourne opines that if
15 the onset of autistic spectrum disorder is delayed
16 until the second year of life that collective medical
17 knowledge to date suggests a triggering event has
18 played a crucial role. He also talked about this
19 during his testimony and used this in terms of the
20 gene environment interaction. How would it be
21 possible for the onset of a disorder like autism to
22 appear later in life if it's not triggered by an
23 environmental factor?

24 A Well, most classic genetic syndromes causing
25 normal development and regression, many of which later

1 lead to death, are storage diseases which are genetic
2 disorders in which the onset of the disorder,
3 basically the risk is present from birth, but the
4 symptoms do not manifest themselves until a later
5 date, sometimes a fairly sudden or precipitous date.

6 Q And that's not because of a specific
7 triggering event or factor?

8 A No.

9 Q Would Rett syndrome be an example of this?

10 A Yes. Rett syndrome is an example of, and
11 this was mentioned earlier, is an example of early
12 normal development, followed by regression in skills.

13 And as mentioned before by Professor Fombonne, it's a
14 *DSM-IV* pervasive developmental disorder or ASD.

15 Development is relatively normal at least in the first
16 six months, typically 12.

17 There's regression typically at 12 to 18
18 months, including social impairment and language
19 impairment which looks very much like the regression
20 in social and language impairment in cases of autism
21 without Rett syndrome where there is regression. And
22 over 80 percent of classic cases are due to mutations
23 in MECP2.

24 There's actually something that's very
25 interesting about finding the gene for Rett disorder.

1 One of the things that's very interesting is that the
2 patient that I saw was atypical in that her head size
3 did not decelerate, as was mentioned previously.
4 Professor Fombonne talked to us about the classic
5 presentation of Rett, which is the only thing we could
6 count on before we had the gene.

7 Now that we can identify girls with Rett
8 disorder because of their mutation, we know, for
9 example, the patient that I saw did not develop some
10 of the neurological signs that Professor Fombonne
11 talked about. The only difference between her and a
12 case of regressive autism is she lost use of her
13 hands. It wasn't really hand-wringing. She just
14 couldn't use them that well.

15 And so I would sort of reassure myself and
16 say, well, girls who have a regression in the typical
17 time of 12 to 18 months with autism who don't lose
18 hand use, they must not have Rett. But as it turns
19 out, there are other girls that don't lose hand use
20 with Rett syndrome. So, in this case, the knowledge
21 of the specific gene in 1999 has contributed to
22 understanding quite a bit more about these patients.

23 Q So, in Rett syndrome, children appear to
24 develop normally. There is no environmental trigger.
25 There's a certain point in time when that gene turns

1 on?

2 A Well, it is a very interesting question, and
3 people like Huda Zoghbi who cloned this gene are doing
4 outstanding work in understanding how this relates to
5 the mechanism not only of Rett disorder but autism
6 more broadly. And the mutation is present from
7 conception, but the expression of the gene only
8 becomes critical in the six- to 18-month timeframe.
9 And not only that, but at the time at which the
10 expression of the gene becomes critical, also it's
11 thought that the symptoms, as mentioned by Professor
12 Fombonne, often follow the change in function of the
13 gene by several months after its key role.

14 For example, it appears to be very important
15 in the maturation of nerve cells, and there are
16 several phases of brain maturation, several of them
17 actually tied to, for example, when there's social
18 smiling, when there's sitting, when language comes in.
19 So there's quite a bit of remodeling of the brain in
20 the first 18 months and particularly most in that time
21 period. And the issue is that the MECP2, which is the
22 gene that's mutated in Rett disorder, only becomes
23 critical in the timeframe of when the symptoms
24 develop.

25 Q So perhaps it would be helpful for a little

1 explanation on how gene expression works. Sort of
2 like a computer program, that everything's sort of
3 preprogrammed and there are specific times that
4 certain genes turn on and turn off?

5 A Right. Right. And I think of it as genes
6 are constantly getting green lights and red lights and
7 some are getting yellow lights to be only partially
8 expressed. So of all the genes that we have, in any
9 given cell in the body at any given time, there's a
10 completely different sort of toggling of what's on and
11 what's off across that pattern.

12 Q So for certain diseases or disorders, if the
13 symptoms of those are not apparent until later on,
14 whether it's autism, that it's within the first couple
15 years of life, or whether another disease like
16 Huntington's where it could be decades later, that
17 doesn't mean that genetics aren't involved, does it?

18 A Huntington's is a classic example of a
19 disorder in which we actually have the problem that we
20 can diagnose with what I think that we would consider
21 certainty in the Court that someone will develop the
22 disease with absolutely no symptoms at say the age of
23 20 but yet know that they will go on to develop the
24 disease by 70. It's a simple genetic disorder, a
25 simple dominant genetic disorder.

1 Q And by simple, is that that one gene is
2 involved?

3 A One gene is involved, and almost everyone
4 who has the gene will develop the disease.

5 Q Okay.

6 A But only decades after conception.

7 Q So there are disorders where it's kind of
8 preprogrammed from birth or from before birth that
9 something will happen, but the expression of that
10 isn't until later?

11 A The only genetic disorders that don't
12 manifest themselves that way lead to death either as
13 miscarriage or as death before birth.

14 Q You said Huntington's is a simple genetic
15 disorder. Would Rett be a simple genetic disorder too
16 because it involves one gene?

17 A Rett is starting to get a little bit more
18 complex because it's not always the same mutation
19 within the gene. So the patient that I described that
20 we had seen actually is missing more of the gene, but
21 because she's missing more of the gene on one
22 chromosome, it looks like that doesn't interfere with
23 the normal chromosome function as much.

24 So given that there are different mutations
25 in the gene, it has some complexity to it so that

1 patients with Rett disorder will vary in terms of the
2 severity of different symptoms. They will also vary
3 in terms of their onset.

4 Q So all genetic disorders aren't similar in
5 complexity?

6 A No, they're certainly not.

7 Q What would be the difference between a
8 simple genetic disorder like Huntington's and a
9 complex genetic disorder?

10 A So a complex disorder, as I said in Rett
11 disorder, we're already getting a little bit more
12 complex because it's one gene but different mutations
13 in different parts of that gene. The next level up
14 would be two genes interacting with each other. And
15 then we get to what we consider complex genetic
16 disorders, which includes Type I diabetes, Type II
17 diabetes. It includes inflammatory bowel disease and
18 definitely includes autism. So although autism is
19 strongly genetic, it is not remotely simple.

20 Q If we can go back for just one moment to the
21 gene environment interaction. In his report, Dr.
22 Kinsbourne cites an article by Purcell in support of
23 his theory that the differential between the
24 concordance for autism of identical and fraternal
25 twins would be observed if autism were entirely due to

1 gene environment interaction. Does the Purcell paper
2 support his statement?

3 A No. The Purcell paper doesn't say anything
4 about autism. It's a simulation or basically
5 mathematical modeling paper referring to a situation
6 much more analogous to what people think of. In fact,
7 the examples they use are major depression where there
8 are known environmental influences and also
9 demonstrated through the same way as autism has its
10 genetic influence, demonstrated genetic influences,
11 but known to be much more of a 50/50 scenario than a
12 90/10 scenario.

13 Q So that's simulation. It's not based on
14 autism, just a mathematical construct?

15 A Yes.

16 Q Okay. Very briefly, on Monday, Dr.
17 Aposhian, Petitioners' toxicologist, testified that
18 there's a subset of the general population that has a
19 genetic hypersusceptibility to mercury injury. Are
20 you familiar with any evidence that would support that
21 statement?

22 A He cited a paper that talked about different
23 metabolism, an effect of mercury, and he cited a
24 relationship with a gene to that. That's not exactly
25 what you're asking, but he was mentioning that I know.

1 And I looked at that paper, and nowhere did it say
2 that the changes that it was seeing were damage as
3 you're using in your question. And also in the paper,
4 it frankly was not a positive association in the
5 paper.

6 Q Recently Petitioners had filed a paper by
7 Beaudet I think is the pronunciation which stated that
8 autism is heritable but not inherited. What is the
9 difference between heritable and inherited?

10 A Well, my esteemed colleague, Professor
11 Beaudet, is trying to make a distinction between
12 genetic risk that gets passed on in terms of genetic
13 variance present in parents to their offspring. He's
14 trying to make a distinction between that and what we
15 would consider de novo abnormalities. So perhaps the
16 best example and one that he uses would be what he's
17 calling heritable I want to call genetic, because
18 heritable makes us think too much about inheritance.

19 So let's just make it simpler and say he's
20 saying if you follow what he says in the paper, he's
21 saying that it's highly genetic. He's not debating
22 that, but he's saying it's not inherited in the sense
23 of risk variance coming from both parents in the sense
24 of most complex genetic disorders.

25 The example that he uses is actually an

1 outstanding one where Down syndrome is the most common
2 genetic cause of intellectual disability. But you
3 heard Professor Fombonne say that the most common
4 inherited cause of intellectual disability is Fragile
5 X syndrome.

6 So how could something be 100 percent
7 genetic in the case of Down syndrome but not
8 inherited? Well, that's because most cases come from
9 a mother who has two chromosome 21s, one of which
10 should go to the offspring, but both go to the
11 offspring, so now the child de novo, meaning nothing
12 was abnormal in the parents that we know of -- there
13 may be risk factors for that passing on of the
14 additional chromosome 21, but the only risk factor we
15 know at this point is maternal age. Older mothers
16 have a higher risk of that.

17 So that is genetic in the case of the
18 typical Down syndrome with three chromosome 21s, but
19 it's not inherited. There is a form of Down syndrome
20 that accounts for 5 percent or so of Down syndrome
21 that has to do with translocations that are inherited
22 from the parent.

23 So in no way is he meaning to minimize the
24 importance of genetics in autism. He's simply
25 highlighting as I have highlighted in previous papers

1 for at least close to a decade in terms of complexity
2 of genetics means that it's not necessarily all
3 inherited like Huntington's, and it's not necessarily
4 all de novo like Down syndrome.

5 Just as Down syndrome has both de novo cases
6 and inherited cases, in autism, we expect a
7 combination of de novo events, in other words,
8 chromosome changes that a child has that a parent does
9 not have, and we also expect a proportion of it to
10 come from something quite a bit more complex than
11 Huntington's but basically genetic variance coming in
12 and contributing to risk.

13 Q So whether the term heritable or inherited
14 is used, it still implies genetics?

15 A It's still genetics.

16 Q Petitioners' experts have talked about
17 certain children being genetically predisposed to have
18 adverse reactions to thimerosal in vaccines or to be
19 genetically predisposed to be unable to clear
20 thimerosal from the body. To your knowledge, is there
21 any support for this genetic predisposition?

22 A It's speculation.

23 Q Okay. In your opinion, I guess based on
24 that, you would believe that members of the scientific
25 medical community who study genetics wouldn't believe

1 that this is an accepted principle at this point in
2 time?

3 A It's certainly not been established.

4 Q Have you had the opportunity to review the
5 records in this case?

6 A Yes.

7 Q Is there any evidence in the record from
8 your review that Michelle Cedillo had a genetic
9 predisposition to react to thimerosal and/or the MMR
10 vaccine?

11 A I see no evidence.

12 Q Did you see the results of any genetic
13 testing in Michelle's records?

14 A I was concerned that genetic tests had not
15 been performed until recently and that in the records,
16 we do not have the results of genetic tests. I would
17 expect and particularly want because of the increased
18 growth and the fact that the length and weight of the
19 child has accelerated in addition to but not as
20 strongly as the head circumference makes it even more
21 important, I think that this is a case where the
22 standard workup should have included a clinical
23 genetic evaluation, at a minimum a chromosomal
24 analysis in terms of autism, FISH or other studies of
25 chromosome 15q11-q13 duplication, Fragile X testing,

1 and then in terms of the increased growth, one should
2 also be looking for mutations in the gene for p10 and
3 also the Sotos syndrome gene.

4 Q Even if Michelle had had genetic testing and
5 if those results were in the record and came back
6 normal, would that rule out a genetic basis for her
7 autism?

8 A No, not at all. We see an over 90 percent
9 genetic contribution of genetics to autism, and I
10 don't know how many cases we will be able to identify
11 once our technology has gone to the point, for
12 example, of complete genome resequencing, which we
13 expect as a medical test in 5, 10 years.

14 What is very clear, what I have witnessed is
15 that even using microscopic tests for chromosomal
16 disorders, we are much better able to detect things
17 than we were 10 years ago, but we are currently
18 literally as we speak in a phase of the resolution of
19 the chromosomal testing going from basically -- the
20 equivalent in telescopes would be from what we could
21 see with a light telescope to there was eventually a
22 shift to basically telescopes using electromagnetic
23 radiation and not light. And we're going through that
24 kind of shift.

25 I don't know what percent we'll have after

1 that. I suspect 20 percent in which we'll be able to
2 identify a known cause at least by the time we've done
3 complete genome resequencing. The issue is that many
4 of the cases if there is an inherited component, which
5 there's a lot of evidence for and not just a genetic
6 de novo component, then one would expect that many of
7 the risk variants may only by themselves confer a
8 slight increase in risk.

9 So then you go, well, if it's only a slight
10 increase in risk, say it's in each individual gene,
11 not the whole together, all together we know that the
12 genes are conferring a lot of increase in risk, if you
13 go, well, who cares if this particular gene only
14 increases risk 8 percent relative to somebody without
15 that variant, my answer for you is that in Type I
16 diabetes, the second strongest gene only increases
17 risk 8 percent, but that gene is insulin.

18 And I must say that I don't think we would
19 be here if we had something as effective in autism in
20 insulin. So the point is weak genetic effects may be
21 powerful indicators of rational development of
22 treatment down the line.

23 Q This morning with Dr. Fombonne's testimony
24 and on cross, there was a lot of discussion about
25 whether this was early onset autism or true regressive

1 autism. Would the opinions you've given today on the
2 genetic basis for autism be any different or would
3 your ultimate opinion that there is no relationship
4 between the vaccines and/or thimerosal and autism
5 differ depending on whether it was early onset autism
6 or true regressive autism?

7 A I'm not sure. Could you restate?

8 Q I don't think I phrased that well. This
9 morning we saw a lot and heard a lot about whether
10 this was early onset, whether her symptoms were seen
11 early on, or whether she regressed after the MMR
12 vaccine. Does that make any difference to your
13 opinion on whether genetics are the most likely -- how
14 important genetics are in the role of autism?

15 A It wouldn't affect the role of genetics as a
16 whole. I guess that's all I would say.

17 Q Okay. It wouldn't really affect your
18 opinion?

19 A No.

20 MS. PATTON: Okay. I don't have any further
21 questions for Dr. Cook.

22 SPECIAL MASTER HASTINGS: Ms. Chin-Caplan,
23 did you have any questions?

24 MS. CHIN-CAPLAN: Yes, I do.

25 SPECIAL MASTER HASTINGS: Please go ahead.

1 CROSS-EXAMINATION

2 BY MS. CHIN-CAPLAN:

3 Q Doctor, you're indicating that autism is a
4 genetic disorder, is that it?

5 A Strongly genetic, yes.

6 Q Strongly genetic. And you talked about
7 single gene defects such as what you would see in
8 Rett's.

9 A Yes. I'm not sure I'd use the word defect,
10 but single gene mutations.

11 Q Single gene mutations. Okay.

12 A I don't like to use the term defect around
13 anyone having autism or intellectual disability.

14 Q Good of you. Single gene defect. And your
15 research has concentrated on the genetic causes,
16 right, of autism?

17 A That's been an emphasis, yes, ma'am.

18 Q And you started that a while ago, didn't
19 you, Doctor, your research?

20 A That's correct.

21 Q For instance, Article 71 in your CV, the
22 International Molecular Genetics Study of Autism
23 Consortium, and it spoke of the further
24 characterization of the autism susceptibility locus,
25 AUTS1, on chromosome 7q, Respondent's Exhibit B.

- 1 A Yes, ma'am.
- 2 Q 71?
- 3 A Yes.
- 4 Q So you were looking on chromosome 7q, is
5 that correct?
- 6 A That's correct. Do you have the paper with
7 you?
- 8 Q No. I'm just asking if that's what your
9 research focused on.
- 10 A That paper is a followup of the previous
11 linkage study. Right.
- 12 Q Okay. And did you find the autism gene on
13 7q?
- 14 A That's something that we are all still
15 looking for.
- 16 Q So you haven't found it yet?
- 17 A Haven't found it and confirmed it yet.
- 18 Q Okay.
- 19 A Actually some of it if I talked to you about
20 I'd get in trouble for sharing what's about to be
21 published.
- 22 Q Well, I wouldn't want you to do that.
- 23 A But I think it's fair to say that we have
24 not gotten to where we're headed there.
- 25 Q Okay. And in 76, again, the International

1 Molecular Genetics Study of Autism Consortium, a
2 genome-wide screen for autism, strong evidence for a
3 linkage to chromosomes 2q, 7q, 16p. Have I read that
4 correctly?

5 A Yes, ma'am.

6 Q Have you found the gene yet on 2q?

7 A We have not found the gene on 2q, but I
8 would say that the evidence that there is a gene there
9 is quite strong. The interesting thing about the
10 evidence on 2q is that initially only our study was
11 finding something there, but then the other studies
12 truly replicated our study by looking at children with
13 language delay, because as been discussed before, not
14 everyone with autism has language delay.

15 Once other studies have emphasized children
16 with language delay, there is strong support across
17 different studies for linkage on 2q. The problem with
18 linkage is you get a linkage signal and then you have
19 a very large region of 10 to 20 million base pairs to
20 map down from, and it's very difficult, and it's very
21 difficult in a complex genetic disorder. So as a
22 matter of fact, we find ourselves in the same position
23 as some of those other disorders I mentioned before
24 such as asthma, such as Type II diabetes.

25 Q So you didn't find it on 2q, and you didn't

1 find it --

2 A We haven't found it yet.

3 Q And you haven't found it yet on 7q.

4 A This is correct.

5 Q Did you find it on 16p?

6 A 16p is another place we are continuing to
7 work. And so in response to you, my answer is we have
8 not found it yet. It is a hard road, and we are
9 continuing to work down it, and we will not tell you
10 that we are sure we have found it until we are sure.

11 Q And then in 82, you're continuing your
12 research in genetics?

13 A Uh-huh.

14 Q And in this one, you talk about an
15 association between a GABRB3 polymorphism and autism?

16 A Yes, ma'am.

17 Q So you're looking at another area of the
18 genome?

19 A This is right. This is a replication of our
20 previous association. This is a completely
21 nonoverlapping sample with the previous study, I don't
22 know what the number is, but also GABRB3, the exact
23 same polymorphism, GABA beta 3 155CA2 in autism, this
24 is an independent replication of that finding. And at
25 the time, we did not consider that polymorphism to be

1 the specific risk variant in autism.

2 We and other groups are continuing to look
3 around that original finding for what specifically in
4 that region confers risk. Again, this puts us in the
5 same position as other disorders. I keep coming back
6 to Type II diabetes.

7 Q And then, Doctor, in the immediate following
8 publication, you're looking at the serotonin
9 transporter gene, the SLC6A4 region in autism.

10 A This is correct.

11 Q So this is like the fifth area of the genome
12 that you're looking for, is that it?

13 A We are looking at the fifth area of the
14 genome because as I mentioned before, the complexity
15 of autism includes multiplicative inheritance with
16 multiple genes conspiring, interacting to cause
17 autism. That is what the twin data suggests when you
18 go up from a 25-fold increase to an over 300-fold
19 increase going from siblings to monozygotic twins. So
20 we expect multiple variants contributing across the
21 genome, which is very similar to what's expected in
22 Type I diabetes and Type II diabetes, asthma and other
23 disorders.

24 Q And then in No. 84, you said FOXP2 is not a
25 major susceptibility gene for autism or specific

1 language impairment. So you discovered one that
2 wasn't one for susceptibility, correct?

3 A Well, it's very interesting about FOXP2
4 because FOXP2 mutations were studied there because
5 it's in the 7q linkage region, so you have to hammer
6 through a lot of genes in those regions. And FOXP2 is
7 particularly interesting because the interest in FOXP2
8 comes from a family that has a complex language
9 disorder with FOXP2 mutations. And since Dr. Monaco
10 had helped find those FOXP2 mutations in those large
11 families with language disorders, this was a logical
12 place to look.

13 I would also add that that study
14 acknowledges and all subsequent studies this
15 outstanding gene to be studied in this linkage region
16 have not been sufficiently tested for involvement.
17 So, in some sense, the statement that it's not a major
18 susceptibility gene for autism susceptibility disorder
19 should say our evidence to date does not support it,
20 but we have not sufficiently done what we need to do
21 to very carefully fine map in that gene.

22 Q And of course the title to this is that it's
23 not a major susceptibility gene for autism or specific
24 language impairment?

25 A Yes, that's correct.

1 Q Okay. So, Doctor, then if you go to the
2 following article, No. 85, you're looking at the
3 receptor gene, HTR2A, in autism, correct?

4 A Correct.

5 Q Is that different from the previous
6 serotonin receptor gene that you were looking at?

7 A Yes. The serotonin transporter gene is
8 different than the serotonin 2A receptor. Those are
9 the two specific genes that our lab headed into
10 because our neurochemical findings of high serotonin
11 in autism pointed to a subset that had high serotonin
12 transport function and another subset that had low
13 5H22A receptor function.

14 And this one if you'd like to know did not
15 provide evidence in support of the serotonin 2A
16 receptor gene, although I would like to point out that
17 a particular hapotide when inherited from one parent
18 or the other was P less than .05, in other words, less
19 than a 5 percent chance of being a false positive.

20 But we considered that that was not
21 sufficiently strong enough evidence to support that as
22 a contributor to autism susceptibility and also
23 pointed out what will need to be done to fully test
24 that and see if that finding that by some standards
25 would -- I mean, less than 5 percent chance that it's

1 not related, we take a conservative approach and say
2 it's not related.

3 Q And in No. 87, Doctor, you looked at the
4 arginine vasopressin receptor 1A or the AVPRIA
5 polymorphism in autism?

6 A That's correct.

7 Q And did you find the gene there?

8 A Well, we actually found evidence for
9 association in one of the polymorphisms. There have
10 been two subsequent studies, and each of the three
11 studies has been positive, and we are actively
12 following that up, partly because of findings of
13 differences in expression of arginine vasopressin
14 receptor 1A having effects on social behavior. So
15 this is an area of continuing investigation.

16 Q And you're continuing the research, and you
17 started looking at Reelin as a candidate gene for
18 autism, and that would be No. 98, correct?

19 A Correct.

20 Q And is Reelin the candidate gene for autism?

21 A Well, a previous group had found evidence
22 for Reelin being involved. And in this study, we did
23 not find evidence to support Reelin.

24 Q Okay. So is Reelin out then? Reelin is not
25 even a candidate any longer?

1 A It's complicated because there are two or
2 more studies at P less than .05 positive, but in our
3 conservative approach to saying whether something
4 contributes to susceptibility, we consider that it
5 might be. And when I say might be, we're talking
6 about --

7 Q Possible?

8 A -- probable as a matter of fact. When you
9 have two or more studies at P less than .05, the most
10 likely thing is the negative studies are false
11 negatives. But recognize we're talking about a
12 stringent level of certainty in the first situation.
13 These are studies where Reelin is mechanistically,
14 biologically plausible because of its role in the
15 development of the brain. The initial study was
16 positive P less than .05, and a subsequent study has
17 been positive.

18 And given the heterogeneity of autism and
19 partly because I'm talking about someone else's
20 finding, and I'm not going to be as hard on them as I
21 would be on myself, we're probably dealing if you want
22 to talk about probability a more than 50 percent
23 chance that it contributes to susceptibility. That's
24 probably where we find ourselves, but we don't
25 consider that an adequate standard to say yes, that is

1 the gene for autism and we found it.

2 Q You said contributes to susceptibility.

3 A Uh-huh.

4 Q You said contributes to susceptibility.

5 A Right.

6 Q Is that an indication that you don't
7 necessarily have to get it?

8 A You don't have to get it? That's part of
9 the complexity. So I mentioned Fragile X syndrome.
10 Twenty-five to 50 percent of patients with Fragile X
11 syndrome have autism. That is an incredibly high rate
12 having that disorder. But all the gene is doing is
13 increasing susceptibility.

14 The one that I know of that I would say
15 susceptibility is approaching 100 percent -- see,
16 susceptibility ranges from something that would be so
17 low you wouldn't consider it a susceptibility factor
18 all the way to 100 percent or near 100 percent for
19 Huntington's. People that have maternally inherited
20 duplications of chromosome 15q11-q13 have 100 percent
21 susceptibility to autism.

22 Q And when they have 100 percent
23 susceptibility, that means that they will get autism?

24 A They develop autism spectrum disorder.

25 Q Okay. But at 50 percent, there's a 50

1 percent chance that you won't get autism, is that it?

2 A Correct.

3 Q And so there's something about this 50
4 percent? Fifty percent of the people will potentially
5 get it, but then there's another 50 percent who may
6 not get it, is that it?

7 A Right. And if you were talking about
8 something that conferred risk in which the population
9 risk was 50 percent, then you would say it's not
10 contributing to susceptibility. But when you're
11 talking about something like autism where the
12 population risk is 1 in 500, then 50 percent is a very
13 large increase in risk.

14 So you think of a term called relative risk.
15 So the relative risk, if something conferred a 50
16 percent risk, the relative risk is 50 percent divided
17 by 1 over 500, and I can't do that math without taking
18 pause, but it's a large number.

19 Q And then, Doctor --

20 SPECIAL MASTER HASTINGS: Before we go on --

21 THE WITNESS: It's actually 250.

22 SPECIAL MASTER HASTINGS: I'm sorry. I
23 interrupted you.

24 THE WITNESS: I interrupted. I'm sorry.

25 SPECIAL MASTER HASTINGS: How do you spell

1 Reelin?

2 THE WITNESS: R-E-E-L-I-N.

3 SPECIAL MASTER HASTINGS: Go ahead.

4 MS. CHIN-CAPLAN: Thank you.

5 BY MS. CHIN-CAPLAN:

6 Q Doctor, in '99, you went back to 2q, and
7 that article indicates that you were looking for nine
8 candidate genes for autism. Did you find it?

9 A I would not say we have found the genetic
10 variation on Chromosome 2q accounting for the
11 significant linkage signal on Chromosome 2q.

12 Q Okay. And then, in 103, you were looking at
13 the functional row of RAB3A and its genomic
14 localization. DNA variants in the human RAB3A gene
15 are not associated with autism. So you found another
16 one that wasn't associated with autism.

17 A That's correct. A lot of work to do;
18 there's a lot of genes.

19 Q A lot of work to do. So then we go to 106,
20 and, in 106, you were looking at the MECP2 structural
21 and 3UTR variance in schizophrenia, autism, and other
22 psychiatric diseases, a possible association with
23 autism. Did you find it? Was there a possible
24 association with autism?

25 A There is a possible association with autism.

1 There have been families published with intellectual
2 disability or autism that convincingly, within those
3 families, there is autism without Rett disorder due to
4 the MECP2 gene, and, in this paper, we provide more
5 support that some patients with autism without Rett
6 disorder may have, at least, as a susceptibility gene,
7 MECP2 playing a role. This is an area of active
8 investigation of geneticists around the world,
9 particularly Dr. Zoghbi, who cloned the Rett gene is
10 very interested in its relationship with autism.

11 Q So this is the gene that is the single-gene
12 defect that we had spoken of earlier for Rett's.

13 A In Rett disorder, it is a single-gene
14 defect. We're looking here at whether it may not be a
15 single gene having such a strong effect that one of
16 the genes that, with other genetic variants,
17 contributes to the disorder.

18 Q Then, Doctor, in 119, you looked at
19 neuroligin 3 and 4.

20 A Yes.

21 Q Did you find the gene there that could be
22 causing autism?

23 A This is an example where we found mutations
24 in neuroligin in 3 and 4, and this had followed a very
25 important paper that had been published in Nature

1 Genetics in terms of finding mutations in neuroligin 3
2 and 4 in autism. These are rare variants.

3 So we have de novo variants that are much
4 more like chromosomal disorders. We have what we
5 consider "common variance." This is the common
6 variance, common disease, view of genetics, and it is
7 the one that is dominant in the field of human
8 genetics and is paying dividends in disorders I keep
9 mentioning, like diabetes, asthma, and inflammatory
10 bowel disease.

11 Studying these genes already through other
12 de novo events in a family with autism and finding
13 mutations that are changing function of the gene, and
14 so this is evidence -- it wouldn't be that these genes
15 are going to be the ones that, say, in 50 percent of
16 people with autism, this gene is active, but it's much
17 more like not so much Fragile X disorder, but less
18 common things than Fragile X disorder that we know
19 from our study of intellectual disability in general
20 are going to add up to contribute to risk.

21 Q Am I right in my thinking, what you just
22 said, that it's not one gene; it's multiple genes that
23 might be adding onto the risk. Is that what you're
24 saying?

25 A Correct.

1 Q So they are all susceptibility genes. Is
2 that it?

3 A That's correct. Some have a stronger effect
4 by themselves than others. Some, by themselves, are
5 sufficient to cause autism.

6 Q But you haven't discovered which one yet.
7 Right?

8 A Oh, no. Fragile X syndrome is one. MECP2
9 is one in terms of autism spectrum disorder. I can go
10 off on a relatively long list: tuberous sclerosis.
11 There are many, many that are not going to account for
12 more than 1 percent of autism but added up account, as
13 was mentioned before already, up to 5 to 10 percent of
14 cases of autism.

15 Q What about the other 90?

16 A So for the other 90 percent, we are in the
17 phase where there is a lot for us to know, nothing
18 that we have had trouble finding to date. I think
19 part of your point is, how many autism genes have you
20 found, Dr. Cook?

21 The reality is that this is a tough thing,
22 and we knew it would be tough going in because, even
23 though the relative risk to siblings is 25-fold
24 greater, this is compared to Type I diabetes, where
25 the increased risk to siblings is 15-fold greater, and

1 the prevalence is one in 500.

2 Many people, I don't think, realize that
3 autism is as prevalent, certainly more severe, even as
4 the father of a child with Type I diabetes than
5 diabetes. It's more prevalent. It's a hugely
6 important health problem, and it's more strongly
7 genetic than diabetes.

8 So the fact that we haven't found them is
9 not surprising. If one gene -- this is the concept of
10 a major gene. If we were dealing with one gene, or if
11 every single case had the same two genes, if every
12 case of autism was the same, and the genetics were
13 simple, then we would have had no trouble finding that
14 gene or those few genes.

15 But from the very beginning, this idea of
16 multiplicative risk, and our estimate that at least
17 five genes will be required, means it's not fivefold
18 increase in risk for one gene and fivefold increase in
19 risk for the next one, all adding up to 25. It's the
20 fifth root of 25, which is only a little bit more than
21 one.

22 Again, you can come back: Why are you
23 looking for genes that, by themselves, only increase
24 it a little bit? Well, because, in the aggregate,
25 they contribute to over 90 percent of the risk for

1 autism and because we keep coming back to -- let's
2 take Type I diabetes where a small effect risk, the
3 kind we're looking at for autism, the kind that, if
4 they were having to find the insulin gene related to
5 diabetes instead of having it thought of as a
6 candidate, they'd still be fine mapping where the
7 insulin gene is. They'd be exactly where we are in
8 autism. And, of course, in diabetes, we've had
9 insulin for quite a while. We don't have it in
10 autism.

11 So that's why we're continuing this effort
12 to find what the specific variants are and to confirm
13 them.

14 Q You continued your work in number 131 where
15 you were looking for the SLC25A12 and CMYA3 gene
16 variants, and you said that those weren't associated
17 with autism.

18 A So the important thing, and this is very
19 important, how the title of this article is worded, so
20 I want to read to the Court the title of 131.

21 Q Okay.

22 A "SLC25A12 and CMYA3 Gene Variants Are Not
23 Associated with Autism in the MSAC Multiplex Family
24 Sample." Now, the reason we emphasize that is because
25 not every sample is identical. We actually enrich for

1 language delay. There are various differences across
2 populations that make genetics different, depending on
3 what sample you have.

4 What's particular notable about this one is
5 there have been two extremely carefully done studies,
6 at least two, that have replicated the SLC25A12 gene's
7 role. This may very well be the gene, under the 2q
8 linkage peak, and I would actually say the evidence
9 for SLC25A12 is approaching the level at which we
10 start calling this one of the confirmed autism-
11 susceptibility genes.

12 But now think about this. We have multiple
13 studies, P less than .05, supporting this, maybe three
14 out of four, and we're still not sure. That's the
15 level of evidence that we need before we're going to
16 say, "Yes, we have that susceptibility gene."

17 So, in some respects, to say, "Haven't you
18 found anything yet?" we are holding this to a very
19 high standard.

20 Q Because you're a scientist. Right?

21 A Because we are scientists, and we do not
22 want to mislead people. The other thing, frankly, is,
23 so we have the gene SLC25A12. Until my colleague,
24 Joseph Buxbaum, or others can translate that knowledge
25 into something that may be helpful and be carefully

1 tested as to whether it's helpful or not, it's not
2 that much to talk about outside of the scientific
3 group.

4 Q Okay. It's fair to state that, as of right
5 now, the title of this article is indicating that it
6 is not associated with autism in the NSAC multiplex
7 family sample.

8 A In that particular sample, yes.

9 Q Okay. Doctor, on 135, you looked at ITGB3.
10 It's associated with serotonin level and autism
11 susceptibility. This seems to be the first time
12 you've used the word "susceptibility" when it comes to
13 autism.

14 A Well, you mentioned susceptibility earlier,
15 and, obviously, I guess that was because I had used
16 the term. So I think if you go back to as early as
17 1995, I had used that term.

18 Q In your articles?

19 A Yes.

20 Q Okay. And then, in 137, you're talking
21 about the genetic interaction between ITGB3 and SLC6A4
22 in autism susceptibility. What did you find about
23 that genetic interaction?

24 A We find that Integrin Beta 3, which is
25 ITGB3, and SLC684, which is the serotonin transporter,

1 are interacting genetically to contribute to autism
2 susceptibility.

3 This follows previous work showing that they
4 interact to contribute to blood serotonin levels,
5 which I mentioned we've been interested in before,
6 and, frankly, this interaction that's both genetic and
7 apparently also physical, I'm very excited about
8 because we came at this through genetics, but, as it
9 turns out, Integrin Beta 3 and serotonin transporter
10 physically interact with each other, and, frankly,
11 this may give us clues as to how to improve treatments
12 that we already have, such as using serotonin
13 transporter inhibitors through a better understanding
14 of the interaction of these two proteins.

15 Q Doctor, one last one. You were looking at
16 Neurexin 1B --

17 SPECIAL MASTER HASTINGS: Which number was
18 that?

19 MS. CHIN-CAPLAN: 143.

20 SPECIAL MASTER HASTINGS: All right. Thank
21 you.

22 BY MS. CHIN-CAPLAN:

23 Q The title is "High Frequency of Neurexin 1
24 Beta, Signal Peptide Structural Variants in Patients
25 with Autism."

1 A Yes. This is a very interesting paper. The
2 reason Neurexin 1 Beta was chosen is because it
3 physically interacts with neuroligin. So neurexin is
4 a protein that comes from the first neuron and
5 interacts with neuroligins coming from the post
6 synaptic neuron.

7 This is a kind of protein-protein
8 interaction that establishes and maintains important
9 synapses, such as GABA and glutamate, which, for
10 various other reasons, we have to think are involved
11 in learning and memory and seizures that may be
12 related to autism.

13 In this case, we found rare variants in
14 terms of mutations affecting function in this gene.
15 It's very interesting because this predated the
16 finding of copy number variation or de novo changes in
17 Neurexin 1 found through copy number variation studies
18 in a recent Nature Genetics paper.

19 Q So, Doctor, would it be fair to state that,
20 right now, there really is no one autism gene?

21 A I would say it would be fair to say there
22 will never be only one autism gene because we already
23 have multiple autism genes in the case of tuberous
24 sclerosis, in the case of Fragile X, and I could go on
25 for a while.

1 Q You've indicated that it's probably multiple
2 autism genes. Is that it?

3 A It's even more complicated than that. So
4 the inherited group with the common variants is
5 multiple genes interacting with each other. Then
6 there is a group of rare variants. Then there is a
7 group of what you would consider chromosomal disorders
8 that are sort of a flavor of the rare-variant forms.
9 So we have at least three forms.

10 Q You spoke earlier of your brother. Had
11 there been some sort of obstetrical environmental
12 injury?

13 A Well, it's very interesting that you ask
14 that because we always referred to him as "brain
15 injured" because the idea was that because of a
16 footling breach birth, that this had contributed to
17 it. This is not a delivery that, after 1961, anyone
18 would have done. It wouldn't be the standard today.

19 The interesting thing about that is that, as
20 it turns out, he has exactly the same syndrome as
21 those that have Chromosome 15q11-q13 duplication in
22 terms of the type of seizure he had, even as
23 eventually having a kind of friendly autism syndrome
24 and having more preoccupations than perhaps social
25 dysfunction.

1 I'm sorry to say that we are now learning,
2 and the parents that are in the organization, the
3 parent-led organization for this syndrome, 15q11-q13
4 duplication, have, unfortunately, become aware of
5 something else that my brother shares with them, which
6 is sudden death in adolescence and young adulthood.

7 So we always thought it was environmental,
8 but I don't know. Looking at him, he has exactly the
9 same syndrome as the patients I see with 15q11-q13
10 duplication.

11 Q Doctor, since you are a doctor, is it
12 possible that your brother could have had a
13 susceptibility gene, and the obstetrical injury
14 triggered this gene to Claire?

15 A Actually, I suspect that there was not an
16 obstetrical injury and that that's basically a red
17 herring for what was a genetic syndrome.

18 Q In the twin studies that you spoke of
19 earlier, is that the Bailey study?

20 A That's the one that I emphasized the most
21 because it was done with such complete ascertainment
22 for the twins. Twin studies have to try to avoid
23 certain kinds of ascertainment biases.

24 Q Doctor, in most twin studies, most
25 "monozygotic twins" meaning they are identical --

1 correct? --

2 A Yes, ma'am.

3 Q -- they share the exact same genes.

4 A There is an exception of the mitochondrial
5 genome. It would round off to 100 percent of genetic
6 variation.

7 Q Okay. There is not 100 percent concordance
8 here, though, is there?

9 A That's correct.

10 Q It's a 60 percent concordance.

11 A Well, the 60 percent concordance for narrow
12 autism.

13 Q True.

14 A And it's important to note that when one
15 includes cognitive disorders and severe social
16 disorders, basically, when one starts to think of
17 autism spectrum disorder, the concordance is 90
18 percent.

19 Q This is where I wonder about this, Doctor,
20 because, say, you have an MS patient, and MS twin
21 studies that have been done, and you have concordance,
22 even there it's only 50 percent, but they don't bring
23 in other people who have neurodemyelinating disorders
24 to raise the rate.

25 Here, what you're saying is 60 percent

1 concordance with a narrow autism disorder, but then
2 you bring in the broader spectrum of related cognitive
3 or social abnormalities. Isn't that a little unusual?

4 A This would be similar to a multiple
5 sclerosis. There would be actually two different ways
6 of doing that study. So, without referring to a
7 specific study, let me talk about how one would get a
8 very similar example to multiple sclerosis.

9 So, very commonly, in multiple sclerosis,
10 you might have a very strict definition where you have
11 to have two demyelinating events.

12 Q But you do.

13 A Pardon me?

14 Q That is the definition of MS.

15 A Okay. Perfect. So, if it requires two
16 demyelinating --

17 Q -- demyelinating events.

18 A Thank you.

19 Q -- welcome -- separated by time and place.

20 A Then the reality is, yes, you will find an
21 increase in people that have a single demyelinating
22 event. You are talking about a spectrum. You are
23 talking about whether you're applying, to some extent,
24 a very rigid diagnostic approach.

25 Autism and autism spectrum are two different

1 things. Autism is actually, from the perspective of
2 being practical in terms of people having impairment,
3 people with autism spectrum have impairment. It's
4 not, oh, a little bit of autism just because you don't
5 meet research diagnostic criteria.

6 We have about 160 people in this country and
7 other countries who are having to struggle with, many
8 of whom are actually doing quite well with -- I don't
9 want everybody to think that this is something that
10 you can't work with in some cases, and I don't want
11 people not to be upbeat about wherever they are.

12 But the point is that when you go from one
13 in 500 to one in 170, or you go to the perspective of
14 saying, "Well, this is a social disorder, but you
15 don't have any intimate relationships," that's a
16 reasonable spectrumed account, yes.

17 This is completely different than in
18 schizophrenia, where basically 50 percent do not have
19 schizophrenic spectrum disorder. This is 90 percent
20 having autism spectrum disorder. So that one in 25
21 that's doing just fine, in a sense, that's the 4
22 percent unaffected.

23 Now, let me get back to the point: The 90
24 percent genetic influence of autism uses the 60
25 percent number. If we use the 92 percent or the 96

1 percent number, heritability would go well into the
2 high nineties. There is no point in that. It's
3 strongly genetic. It's not purely genetic.

4 Q Strongly genetic but not purely genetic.
5 There's environmental influences then.

6 A Well, we don't know what the other 8 percent
7 is.

8 Q Eight percent. If you bring it up to 92
9 percent after bringing in all of the associated
10 disorders.

11 A Ninety percent genetic, the other 8 percent
12 is other.

13 Q Doctor, this is Respondent Exhibit P, Tab 4.
14 It's the Bailey study: "Autism as a Strongly Genetic
15 Disorder." He cited it in his report.

16 A Okay.

17 Q Okay. Just a few questions here, Doctor.
18 We had discussed earlier the potential of a
19 contributing factor from obstetrical environmental
20 causes. Doctor, can you take a look at page 64 of
21 this article, at the very bottom, the sentence
22 starting with "Consequently," right-hand side?

23 A Yes.

24 Q Okay. It says: "Consequently, despite the
25 evidence for strong genetic influences, both groups

1 implicated obstetric hazards as environmentally
2 determined etiological factors in some pairs, possibly
3 leading to an excess of autistic twins in the
4 Scandinavian series."

5 Doctor, I read that statement, and I think
6 to myself, okay, they have a susceptibility gene, and
7 the obstetrical hazard that occurred environmentally
8 affected the outcome.

9 A That would be incorrect. What they are
10 saying here is that obstetrical hazards are accounting
11 for why the concordance is not 100 percent.

12 Q I'm sorry. I missed that.

13 A In other words, in twins in general there
14 are more obstetrical hazards, and so it is not always
15 equal between the two identical twins. So, in some
16 cases, there is much less fetal growth in one twin as
17 opposed to the other, and what they are saying is that
18 that accounts actually for the discordant twins.

19 So, basically, what they are talking about
20 is the environmental influence. We're talking about
21 this 8 percent. Much of that is related to
22 obstetrical and prenatal events.

23 Q Okay. Then further on, that sentence says:
24 "Gilbert has suggested that only the minority of
25 cases that the family history of autism of Asperger's

1 syndrome represent a genetic form of the disorder, the
2 majority being a consequence of obstetric hazards or
3 medical disorders."

4 SPECIAL MASTER HASTINGS: Can you tell me
5 where you were reading from there?

6 MS. CHIN-CAPLAN: I'm on the bottom of 64 to
7 the top of 65.

8 SPECIAL MASTER HASTINGS: Which attachment
9 was that?

10 MS. CHIN-CAPLAN: This is Respondent P, Tab
11 4, and I'm on page 64.

12 SPECIAL MASTER HASTINGS: And what's the
13 name?

14 MS. CHIN-CAPLAN: This article is called
15 "Autism as a Strongly Genetic Disorder: Evidence from
16 a British Twin Study."

17 SPECIAL MASTER HASTINGS: It's Tab 5, not
18 Tab 4?

19 MS. CHIN-CAPLAN: I'm sorry. Tab 5. It's a
20 long day.

21 SPECIAL MASTER HASTINGS: Okay. And you're
22 on 64 where?

23 MS. CHIN-CAPLAN: Into 65.

24 SPECIAL MASTER HASTINGS: Okay. Go ahead.

25 BY MS. CHIN-CAPLAN:

1 Q So I read that correctly, Doctor. Right?

2 A Yes. You read a citation of Bailey of a
3 previous study by Gilbert.

4 Q Right. Does Gilbert say that Asperger's
5 represents the genetic form of autism, and the rest
6 are a consequence of obstetric hazards from medical
7 disorders?

8 A Well, all I can do is tell you that this
9 paper cites Gilbert to that effect. I don't have the
10 Gilbert paper in front of me.

11 Q Okay.

12 A I have to point out that what Gilbert would
13 be referring to, in terms of medical disorders, would
14 include things that we would consider genetic but not
15 inherited. This gets back to this previous discussion
16 about what Art Beaudet said. So, under "medical
17 disorders," he would be including things like tuberous
18 sclerosis that are known to be genetic.

19 Q Then, Doctor, if you go on to page 67, and
20 it talks about the follow-up of the original pairs,
21 nine lines down, beginning with "None." It states:
22 "None of the five monozygotic co-twins have been
23 diagnosed as autistic in childhood, and only one had
24 an autistic-like disorder." Have I read that
25 correctly?

1 A Yes.

2 Q So it sounds like, Doctor, that simply
3 because you are a monozygotic twin doesn't mean that
4 you will necessarily come down with autism. Correct?

5 A Do you mean if one twin has autism, it is
6 not 100 percent likely that the other monozygotic twin
7 will have autism.

8 Q Correct.

9 A Correct. That's what I meant by saying it's
10 a 60 percent risk.

11 Q Doctor, is your point that these are all
12 gene-to-gene interactions? Is that it, the cause of
13 the autism?

14 A No. Sometimes single genes, a very strong
15 effect; gene interaction with genes; and also
16 environmental contributions.

17 Q When you say "environmental contributions,"
18 what do you mean?

19 A I mean everything ranging from things like
20 maternal age at birth is an environmental
21 contribution. So the environment has to do with the
22 fact that, frankly, the egg is older, and it's harder
23 to maintain homeostasis in the egg. It seems to be
24 that the paternal age has been implicated as an
25 environmental factor.

1 These are both preconception environmental
2 factors. It could range all the way up to whatever
3 time in which you think there is an onset, but the
4 point is that the number of potential environmental
5 factors and their timing precedes conception.

6 Q So is it your point that you can never get a
7 postpartum type of autism?

8 A Post-delivery?

9 Q Yes.

10 A No. There is a series of cases in Tanzania
11 where it appeared that malaria contributed.

12 Q So infectious causes.

13 A Uh-huh.

14 Q How about anoxia, Doctor?

15 A The studies on anoxia have implicated much
16 more motor skills impairment rather than autism.

17 Q So, Doctor, what if I told you that a child
18 had had an MMR, suffered a seizure, became
19 encephalopathic, and then developed autistic symptoms.
20 Would that be implausible?

21 A You just told me something that occurred,
22 and you're saying that somebody had an MMR
23 vaccination, they had a seizure, they became
24 encephalopathic, and then they had autism.

25 Q Uh-huh.

1 A Okay. You just told me something that
2 happened. Could that happen? Yes. In fact, any time
3 between 12 and 18 months, which we know to be a time
4 of regression in autism, you could have also told me -
5 - the whole point is you're wanting me to say, yes,
6 there is some relationship with MMR vaccination. The
7 point is, kids between 12 and 18 months are having
8 vaccinations.

9 Now, the reason that I'm not going to
10 acknowledge what you're asking -- in other words,
11 there is a relationship between the MMR vaccination
12 and what happened later -- is because that is the same
13 logic that was used to blame mothers for causing
14 autism because there is a mother, they take care of
15 their child, and they develop autism. It's exactly
16 the same logic.

17 Q Would it surprise you if this Court has
18 awarded compensation under that very scenario?

19 A On what scenario?

20 Q On the very scenario that I just related to
21 you.

22 A The scenario that you related to me. Would
23 it surprise me? That's a tough question. I don't
24 know enough about the Court and its history to answer
25 one way or the other.

1 Q Fair enough. Doctor, are you aware that IOM
2 held a meeting in April of this year on autism and the
3 environment?

4 A I'm aware of a meeting, yes.

5 Q Did you attend?

6 A No, I did not.

7 Q Doctor, at this meeting, they were looking
8 at potential environmental causes of autism, weren't
9 they? One of those presentations was "How May
10 Environmental Factors Impact Potential Molecular and
11 Epigenetic Mechanisms?" and it was by, I think, Dr.
12 Beaudet.

13 A I could imagine him giving that
14 presentation. I did not attend, so if you want me to
15 comment on this --

16 MS. CHIN-CAPLAN: Petitioners' Exhibit 76.

17 SPECIAL MASTER HASTINGS: Okay. Thank you.

18 MS. CHIN-CAPLAN: You're welcome.

19 BY MS. CHIN-CAPLAN:

20 Q How about this one? "Environmental
21 Epidemiologic --"

22 SPECIAL MASTER HASTINGS: What are you
23 reading from? Are you reading from that Exhibit 76?

24 MS. CHIN-CAPLAN: Yes. It was all bound
25 together.

1 THE WITNESS: If I'm going to be asked about
2 Professor Beaudet's presentation, I would like to
3 comment on the presentation and see it.

4 MR. MATANOSKI: Actually, there was no
5 question.

6 SPECIAL MASTER HASTINGS: Right. I don't
7 think there has been any question yet, so you'll have
8 to wait until you get a question.

9 You're going to start to read from Exhibit
10 76.

11 MS. CHIN-CAPLAN: Correct.

12 SPECIAL MASTER HASTINGS: Could you tell me
13 what page number it is?

14 MS. CHIN-CAPLAN: They were presentations.

15 SPECIAL MASTER HASTINGS: There's no tabs in
16 Exhibit 76.

17 MS. CHIN-CAPLAN: They were all
18 presentations by different individuals at the IOM
19 conference.

20 SPECIAL MASTER HASTINGS: I see pages. I'm
21 looking at Exhibit 76. Do you have it in front of
22 you, Mr. Shoemaker? I can't believe I got to it
23 faster than you did. But it's got page numbers on it,
24 the electronic version that you folks filed, so it
25 does have page numbers.

1 MR. SHOEMAKER: I have it broken out by the
2 presentation of all of the different tabs.

3 MS. CHIN-CAPLAN: We did not number them,
4 Special Master.

5 SPECIAL MASTER HASTINGS: So you don't have
6 the copy that you filed.

7 MR. SHOEMAKER: Not of the whole thing put
8 together. I just have the presentation and the
9 various tabs.

10 SPECIAL MASTER HASTINGS: Okay. How long of
11 a document is it? Okay. The presentation; who is it
12 by?

13 MS. CHIN-CAPLAN: This one is by Irva Hertz
14 Piccioto --

15 SPECIAL MASTER HASTINGS: Okay.

16 MS. CHIN-CAPLAN: -- and it's entitled
17 "Environmental Epidemiology Studies: New Techniques
18 and Technologies To Find Environmental Triggers."

19 MS. PATTON: We don't have a copy of that
20 with us. We don't have every one of the exhibits you
21 filed in the courtroom here.

22 MS. CHIN-CAPLAN: This is the only one I
23 have. I'll be glad to show it to you.

24 MS. PATTON: If you're going to ask Doctor -
25 -

1 MS. CHIN-CAPLAN: I'm not going to ask him
2 any questions, no. I'm just asking him if --

3 SPECIAL MASTER HASTINGS: Go ahead. Ask him
4 a question.

5 MR. MATANOSKI: Wait. Just a minute, Your
6 Honor. You're not going to ask him any questions?

7 MS. CHIN-CAPLAN: I'm asking him if this is
8 what was presented at IOM.

9 MR. MATANOSKI: He said he wasn't there.
10 How can he even answer the question?

11 MS. CHIN-CAPLAN: Well, let me ask this
12 question.

13 MR. SHOEMAKER: I'm sorry. Which
14 presentation was that? I found a list of the letters
15 of the presentations.

16 SPECIAL MASTER HASTINGS: Yes. Hertz
17 Piccioto.

18 MR. SHOEMAKER: That's Tab I.

19 SPECIAL MASTER HASTINGS: Yes.

20 MR. SHOEMAKER: I'll bring it up.

21 SPECIAL MASTER HASTINGS: What question are
22 you going to ask him?

23 BY MS. CHIN-CAPLAN:

24 Q Doctor, let me ask you this question. You
25 didn't attend the conference. Is that true?

1 A That's correct.

2 Q And the topic of that was environmental
3 causes of autism. Isn't that true?

4 A My recollection is something -- I don't know
5 that that's the exact title, but I know there was a
6 meeting about that.

7 Q So would it be fair to state that there is a
8 number of people who disagree with you that autism is
9 a purely genetic disorder?

10 A I never said that autism was a purely
11 genetic disorder. I said it was a strongly genetic
12 disorder.

13 Q And is it influenced by environmental
14 factors?

15 A It is likely to be influenced by
16 environmental factors. The challenging thing, in
17 terms of studying environmental factors in autism, is
18 because the effect is relatively weak, so the
19 epidemiological studies that have been done have had
20 difficulty in confirming factors that have come up.

21 Q Thank you. Doctor, would you agree that the
22 rate of autism has increased within the past 20 years
23 or so?

24 A The measured prevalence of autism increased.
25 The real rate of autism has not been confirmed to

1 increase, to my belief.

2 Q So, in your mind, it has not increased. Is
3 that what you're saying?

4 A The measured prevalence has increased, but
5 no one has demonstrated that there has been a real
6 increase other than by changing and definition and
7 particularly by changing in ascertainment of the rate.

8 Q So if you assume that there was an epidemic,
9 would it be fair to state that you don't get an
10 epidemic from genetic causes within one generation?

11 A Well, the first thing is we have to think
12 about what we consider an epidemic, and if, by
13 "epidemic," we mean something that is much more
14 important and common than previously assumed to be,
15 then autism is an epidemic.

16 If you are asking, is autism related to an
17 increase in rate, I do not believe that that has been
18 shown to be a real increase in rate, and I have much
19 personal experience as to the spurious nature of that
20 increase. Again, it's an epidemic from the sense of
21 it's much more important than previously recognized.

22 The families that I have been treating, many
23 of whom were not able to get a diagnosis before I saw
24 them because we did not have the careful research
25 diagnostic criteria, and, frankly, in Chicago, we had

1 a logical fallacy where the two major places that
2 would have diagnosed autism, one of them said, Oh, you
3 have an intellectual disability; you don't have
4 autism; you have intellectual disability. Then if
5 they would see somebody with autism who didn't have
6 intellectual disability, they would say, Well, you
7 can't have autism because you don't have intellectual
8 disability.

9 That is not a systemic approach to
10 diagnosis, so I'm not willing to grant the assumption
11 that there is an epidemic in the sense of a real
12 increase in prevalence.

13 In addition, Illinois is often cited as
14 having an increase in cases in the educational system,
15 and I was involved in a task force in 1986 that
16 allowed children in Illinois to be classified as
17 having autism. So, of course, it went up 14,000
18 percent because you couldn't have autism in Illinois
19 in the school district until we changed that in 1986.

20 Q Doctor, you wrote an article, or you're one
21 of the co-authors of an article, about maternal
22 smoking during pregnancy and severe antisocial
23 behavior in offspring.

24 A Yes.

25 Q It was a review.

1 A It's a review article.

2 Q Doctor, based on your review of the
3 literature -- is that it? -- your conclusion was,
4 "Existing evidence provides consistent support for,
5 but not proof of, an etiologic role for prenatal
6 smoking in the onset of antisocial behavior." That
7 was your conclusion, wasn't it?

8 A Yes.

9 Q And that was just based on a review of the
10 literature.

11 A The conclusion was based on research studies
12 that had carefully demonstrated that. And I'm
13 continuing to collaborate with my colleague, Dr. Loren
14 Wauchslog, on careful studies to further make sure --
15 in this case, it's very interesting -- to make sure
16 that that is an environmental influence and not
17 something that's subtly influenced by genetics
18 instead of environment.

19 Q Okay. Doctor, just one last --

20 SPECIAL MASTER HASTINGS: Before you move
21 on, what were you just reading from?

22 MS. CHIN-CAPLAN: Some research that we had
23 done.

24 SPECIAL MASTER HASTINGS: Okay. Nothing
25 that's in the record?

1 MS. CHIN-CAPLAN: Nothing that's in the
2 record.

3 SPECIAL MASTER HASTINGS: All right.

4 BY MS. CHIN-CAPLAN:

5 Q Doctor, just one last question. If somebody
6 had an inherited immune deficiency and was
7 asymptomatic and received a vaccine and the immune
8 deficiency flared, in your opinion, would the vaccine
9 be an environmental trigger of the flaring of that
10 disorder?

11 A Well, the situation that you're asking me
12 about is implausible in the sense that if somebody has
13 an immune deficiency, they would have been exposed to
14 many environmental agents before the time of
15 vaccination, and one would have expected symptoms
16 before that. So now the idea of it triggering the
17 onset of the disorder would not make sense.

18 Q And you weren't here for Dr. Koettinger's
19 presentation, were you?

20 A No, I wasn't. Sorry.

21 MS. CHIN-CAPLAN: Thank you, Doctor.

22 SPECIAL MASTER HASTINGS: You're done, Ms.
23 Chin-Caplan?

24 MS. CHIN-CAPLAN: I am, Special Master.

25 SPECIAL MASTER HASTINGS: Any questions for

1 this witness? Go for it.

2 SPECIAL MASTER VOWELL: Doctor Cook, in your
3 report, the analogy of gene expression is looking down
4 a road and seeing traffic lights that were green and
5 red. Well, to continue that analogy, certain things
6 turn those lights green or red. It may be a car
7 parked at an intersection, triggering a sensor. It
8 might be speeding vehicles. It might be timers. Can
9 environmental things trigger a gene expression?

10 THE WITNESS: Environmental events can
11 trigger changes in gene expression, yes. Your
12 analogies would all be true. All of the same ways in
13 which those lights might be turned on and off --

14 SPECIAL MASTER VOWELL: So the timer would
15 be Huntington's.

16 THE WITNESS: Huntington's would be the
17 timer analogy. It also could be, as you say, cars
18 passing sensors, would be more the example of
19 something perhaps in the environment changing. I'm
20 sorry.

21 To follow up, actually, I think a lot of
22 that signaling has to do with another concept of
23 environment in development of the brain, is that the
24 environment of each cell is changing as that cell may
25 be migrating through the brain as it may be shifting

1 from the environment of the less-mature brain to a
2 more mature brain, is also helping turn on and off.

3 SPECIAL MASTER VOWELL: One of the
4 Petitioners' expert witnesses referred to an article
5 by Herbert, which is at Exhibit 61, Tab FF, Martha
6 Herbert in Clinical Neuropsychiatry: "Autism: A
7 Brain Disorder or a Disorder That Affects the Brain?"
8 is the title. Are you familiar with this article,
9 Doctor?

10 THE WITNESS: Just in passing, more having
11 heard it cited.

12 SPECIAL MASTER VOWELL: Do you have any
13 comments on it? Her approach seems to be that there
14 are environmental factors in this strongly genetic
15 disease or syndrome.

16 THE WITNESS: I thought it was a
17 comprehensive review, in looking at all potential
18 possibilities. So I think she was putting, side by
19 side, the chance of probably even a more pure genetic
20 causation than we have, side by side with some
21 alternative interaction concepts. So in this context
22 review article, I think it's good to think about all
23 possibilities.

24 If you look at the possibilities represented
25 in a couple of tables from that -- let me see if I

1 can. If you look at Table 1 on page 356, two disease
2 models, we can find quite a few manifestations, in a
3 sense, of different models, and I think actually the
4 model of strongly genetic, brain-based -- both of the
5 models are extremely complex. I must say, when you
6 come up with complex possibilities to explain autism,
7 you're getting close to what's happening. If this was
8 simple, we would be a lot further along to
9 understanding it.

10 The one thing that's good here is, if you
11 read this, it's hard to -- I've heard this article
12 quoted quite a bit as just having one idea being
13 posited from it, but it's incredibly complex, and,
14 again, we are dealing with a complex developmental
15 neurobiological syndrome.

16 SPECIAL MASTER HASTINGS: Anything further?
17 Do you have any questions?

18 Any redirect for this witness?

19 MR. MATANOSKI: I just have one question.

20 SPECIAL MASTER HASTINGS: Go for it.

21 REDIRECT EXAMINATION

22 BY MS PATTON:

23 Q Dr. Cook, in the early part of the cross,
24 Petitioners' counsel seems to imply with the questions
25 that you're running a little behind schedule in

1 finding the genes that cause autism. How many areas
2 are there on the human genome?

3 A I'm sorry. How many areas?

4 Q How many genes are involved?

5 A I guess it just got reset to 20,000 genes,
6 and the one thing I didn't point out is that we're
7 quite excited. What's happened in the study of genes
8 is that some of the things that we were doing that
9 might take us another five years are rapidly changing
10 now that there are whole genome associations, and
11 we're eagerly anticipating the results of those first
12 whole genome association studies in autism. It will
13 be similar to other disorders that have been hard to
14 pin down the genetic variants and have led to a
15 plethora of publications in Science and Nature
16 recently on disorders like diabetes.

17 So we now have tools to not do linkage and
18 then spend 10 years following up but to look at a
19 million markers in the genome to be able to pinpoint
20 almost all of the genetic variation in one experiment.

21 SPECIAL MASTER VOWELL: Thank you.

22 SPECIAL MASTER HASTINGS: Anything further?

23 MS. CHIN-CAPLAN: No, Special Master.

24 SPECIAL MASTER HASTINGS: All right. Thank
25 you, Dr. Cook. We appreciate your testimony.

1 (Witness excused.)

2 SPECIAL MASTER HASTINGS: With that, we're
3 done for the day, and we'll start at 9 a.m. tomorrow
4 with Dr. Wiznitzer's testimony. Is that right, Mr.
5 Matanoski? Dr. Wiznitzer tomorrow?

6 MR. MATANOSKI: Yes, sir.

7 SPECIAL MASTER HASTINGS: And that will be
8 the only witness for tomorrow.

9 MR. MATANOSKI: That's correct, sir.

10 SPECIAL MASTER HASTINGS: All right. At 9
11 a.m. tomorrow, we'll start. We're adjourned today.

12 (Whereupon, at 6:37 p.m., the hearing in the
13 above-entitled matter was adjourned, to be reconvened
14 Tuesday, June 19, 2007, at 9:00 a.m.)

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REPORTER'S CERTIFICATE

DOCKET NO.: 98-916V
CASE TITLE: Theresa Cedillo v. HHS
HEARING DATE: June 18, 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 18, 2007

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